UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES AND
TOXIC SUBSTANCES

January 31, 2001

MEMORANDUM

SUBJECT: Endosulfan: HED Risk Assessment for the Endosulfan Reregistration Eligibility Decision (RED) Document. Chemical No. 079401. Case No. 0014. Barcode D250471.

FROM: Diana Locke, Ph.D.
Reregistration Branch II,
Health Effects Division (7509C)

THRU: Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)

TO: Richard Dumas, Acting Chief
Special Review Branch
Special Review and Reregistration Division (7508W)

The attached review of the Human Health Assessment for the endosulfan Reregistration Eligibility Decision (RED) document was generated as part of Phase 2 of the Proposed Public Participation Process. The Health Effects Division's (HED) chapter reflects revisions made in keeping with the Phase 1 comments, the Agency's current guidelines concerning the retention of the Food Quality Protection Act (FQPA) factor and the risk assessment, and includes the results of a dietary risk evaluation using United States Department of Agriculture's (USDA) 1989-1992 consumption data and Dietary Exposure Evaluation Model (DEEM™) software. This chapter includes a summary of the product chemistry from Ken Dockter, residue chemistry from John Punzi, toxicology review from Nicole Paquette/David Liem/Elizabeth Mendez, occupational exposure from Renee Sandvig, acute and chronic DEEM calculations and dietary risk

characterization from Sherrie (Mason) Kinard, drinking water exposures from Nelson Thurman, et al. [Environmental Fate and Effects Division (EFED)], as well as risk assessment and risk characterization from Diana Locke.

cc: Stacey Milan
Margaret Stasikowski
Lois Rossi
Pauline Wagner

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY 5

2.0 PHYSICOCHEMICAL PROPERTIES CHARACTERIZATION 10

3.0 HAZARD CHARACTERIZATION 12
- 3.1 Hazard Profile 12
- 3.2 Pharmacokinetics 15
- 3.3 Acute Toxicity 15
- 3.4 Subchronic and Chronic Toxicity 16
- 3.5 FQPA Considerations 21
- 3.6 Dose Selection 22
  - 3.6.1 Acute Reference Dose (RfD) 23
  - 3.6.2 Chronic RfD 24
  - 3.6.3 Dermal Absorption 26
  - 3.6.4 Short-term (1-30 days) Dermal Occupational Exposures 27
  - 3.6.5 Intermediate (one to several months)/Long (several months to 1 year)-term Dermal Occupational Exposures 28
  - 3.6.6 Short-term (1-30 days) Inhalation Occupational Exposures 28
  - 3.6.7 Intermediate (one to several months)/Long (several months to 1 year)-Term Inhalation Occupational Exposures 30
  - 3.6.8 Carcinogenic Potential 30
- 3.7 Endocrine Disruption 33

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION 35
- 4.1 Summary of Registered Uses 35
- 4.2 Dietary Exposure/Risk Pathway 37
  - 4.2.1 Residue Profile 37
  - 4.2.2 Acute Dietary 38
  - 4.2.3 Chronic Dietary 40
  - 4.2.4 Cancer Dietary 42
- 4.3 Drinking Water Exposure/Risk Pathway 42
  - 4.3.1 Ground Water Resources 44
  - 4.3.2 Surface Water Resources 44
  - 4.3.3 Estimated Environmental Concentrations 45
  - 4.3.4 Drinking Water Levels of Comparison 46
- 4.4 Residential Exposure/Risk Pathway 49
  - 4.4.1 Home and Recreational Uses 49
  - 4.4.2 Other 49

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION 50

5.1 Overview 50
5.2 Acute Risk 51
5.2.1 Aggregate Acute Risk Assessment 51
5.2.2 Acute DWLOC Calculations 52
5.3 Short- and Intermediate-term Aggregate Risk 53
5.4 Chronic Risk 53
5.4.1 Aggregate Chronic Risk Assessment 53
5.4.2 Chronic DWLOC Calculations 53

6.0 CUMULATIVE RISK 54

7.0 OCCUPATIONAL EXPOSURE 54
7.1 Handler 54
7.2 Postapplication 56
7.3 Non-occupational Exposures 59
7.4 Incident Data 59

8.0 DATA NEEDS/LABEL REQUIREMENTS 59
8.1 Toxicology 60
8.2 Product Chemistry 60
8.3 Residue Chemistry 60
8.4 Occupational Exposure 60

9.0 REFERENCES AND ATTACHMENTS 70
9.1 Attachments 70
9.2 References 70

1.0 EXECUTIVE SUMMARY

Endosulfan (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide) a dioxathiepin (broadly classified as organochlorine), is a broad spectrum contact insecticide and acaricide that is used on a wide variety of vegetables, fruits, cereals, and cotton, as well as ornamental shrubs, trees, vines, and ornamental herbaceous plants in commercial agricultural settings. Technical grade endosulfan is composed of two stereochemical isomers: á-endosulfan and â-endosulfan, in concentrations of approximately 70% and 30%, respectively.

Endosulfan is formulated for occupational use as a technical grade manufacturing product (95% active ingredient [ai]), emulsifiable concentrate (9 - 34% ai), and a wettable powder (1 - 50% ai). The wettable powder is frequently packaged in water soluble bags. It should be noted that the Endosulfan Task Force (Aventis Crop Science USA LP, FMC Corporation, and Makhteshim-Agan of North America, Inc.), who are the primary data-submitters but not the sole registrants, are not supporting several crop, residential, and smoke canister uses, as well as dusts and aerosols. Based on the outcome of the four 6F Notices (02/05/97, 02/13/97, 03/18/98, and 07/19/00) issued by the Agency, which received no dissenting comments and have been finalized, the risk assessment was revised to exclude the uses subject to those Notices. Depending on the crop to be treated and the formulation to be used, formulations containing endosulfan may be applied by groundboom sprayer, fixed-wing aircraft, chemigation (potatoes only), airblast sprayer, rights of way sprayer, low pressure handwand, high pressure handwand, backpack sprayer, and dip treatment. The number of allowable applications varies, depending upon use. On the majority of product labels, the number of maximum allowable applications ranges between 1 and 3 per season or year, and does not exceed 5. Over 50 food tolerances have been established for residues of endosulfan in or on various plant and animal commodities, and range from 0.1 ppm to 24 ppm. The current tolerance expression includes endosulfan (á- and â- isomers) and endosulfan sulfate (a plant, animal, and environmental metabolite of toxicological concern).

Due to the availability/submission of acceptable/guideline oral, dermal, and inhalation studies using endosulfan, the dietary and occupational risk assessments were conducted using route-specific endpoints. The acute dietary endpoint is based primarily on neurotoxicity. The neurotoxicity is believed to result from over-stimulation of the central nervous system. Characteristic clinical signs of endosulfan-induced neurotoxicity include, in part: hyperactivity, tonic contractions, involuntary muscle movements, pronounced sensitivity to noise and light, incoordination, seizures, and convulsions. These clinical signs are observed in humans accidentally exposed to endosulfan, and in animal studies of varying treatment durations following different routes of exposure and in different animal species. The chronic dietary, and short-, intermediate-, and long-term dermal and inhalation endpoints are based on the toxic effects observed in animals following subchronic or chronic exposure , and include: neurotoxicity, hematological effects, and nephrotoxicity. In some rodent studies, endosulfan inhibited plasma cholinesterase at the highest doses tested. Endosulfan is not a dermal sensitizer, nor is it mutagenic or carcinogenic (“not likely” a human carcinogen).

The endosulfan residues of toxicological concern are: á-endosulfan, â-endosulfan, and endosulfan sulfate. For purposes of conducting the endosulfan risk assessment, the Agency assumed that the 3 residues of toxicological concern are approximately equal in toxicity. To fully characterize the hazard and subsequent potential risk from exposures to endosulfan, subchronic neurotoxicity and developmental neurotoxicity studies are needed. The potential for endosulfan to cause changes in endocrine function that lead to adverse effects was evaluated from the results of the submitted guideline studies and available published studies. In the process of this evaluation, endosulfan was identified as a potential endocrine disruptor. A developmental neurotoxicity study is requested. A preliminary review of arguments submitted by the Endosulfan Task Force (ETF) did not give the Agency reason to change its finding. The Agency is in the process of developing criteria for characterizing and testing endocrine disrupting chemicals and plans to implement an Endocrine Disruptor Screening Program in 2001. Endosulfan will be reevaluated at that time and additional testing may be requested.

For ease of discussion, unless specifically indicated, the exposure and risk assessment review will refer to á-endosulfan, â-endosulfan, and endosulfan sulfate, collectively as "endosulfan."

No evidence of quantitative sensitivity to endosulfan exposure was reported for fetus/offspring in the guideline developmental and reproductive toxicity studies. However, results from the reproductive study raise a possible qualitative concern regarding special sensitivity. In the reproduction study, the effects seen in the female offspring of the F_0 generation (increased pituitary) and F_{1b} generation (increased uterine weights) that occurred at the high-dose may be of greater severity than the toxicity observed in parental animals (decreased body weight). In addition, results from an open literature study suggest special sensitivity; therefore, the FQPA Safety Factor Committee concluded that the FQPA safety factor is required based on the suggestive special sensitivity and the uncertainty associated with the data gap (subchronic neurotoxicity and developmental neurotoxicity studies are requested), but can be reduced from 10x to 3x because: 1) there is no evidence of increased susceptibility in any submitted study; 2) the severity of the fetal effects in the reproductive toxicity study were not consistent between generations and the target organ toxicity seen in this study was not seen in any other study; and 3) reliable data and conservative assumptions were used to assess the potential dietary (food and water) exposure to this chemical. For purposes of assessing the risks posed by endosulfan, the 3x factor was applied to the acute and chronic dietary assessments, for only those subgroups that are comprised of infants, children, and females of child-bearing age (i.e., women who may be pregnant or may become pregnant). The FQPA safety factor for the general population was removed (i.e., reduced to 1x).

Exposure to endosulfan residues of toxicological concern that may occur from consumption of foods was estimated for dietary exposures that can occur over a single-day (i.e., acute) or longer (chronic), up to a lifetime. These analyses were conducted using Dietary Exposure Evaluation Model (DEEM^{TM}) version 7software for the general population and for numerous population subgroups, including infants, children, and females of child-bearing age (i.e.,

females between 13 to 50 years of age). The acute dietary exposure assessments were conducted using probabilistic methodologies. The Tier 3 dietary exposure analyses incorporated residue estimates based largely on: percent crop treated (%CT) estimates provided by the Biological and Economic Analysis Division (BEAD); data obtained from the Food and Drug Administration's (FDA) monitoring program, the United States Department of Agriculture's (USDA) Pesticide Data Program (PDP); and, to a lesser extent, field trial data, and tolerance values. The residue estimates, along with data from the USDA's 1989-1992 Continuing Survey of Food Intake by Individuals (CSFII) food consumption survey, were used to determine the exposure to food of the various population subgroups. To assess risks from consumption of foods containing endosulfan residues, the estimated acute and chronic dietary food exposures for the U.S. general population were compared to the acute and chronic population adjusted doses (PADs) of 0.015 mg/kg/day (aPAD) and 0.006 mg/kg/day (cPAD), respectively. The estimated acute and chronic dietary food exposure to subgroups comprised of infants, children or females of child bearing age were compared to an aPAD of 0.005 mg/kg/day and a cPAD of 0.002 mg/kg/day, respectively.

The Agency is currently developing new procedures for handling FDA surveillance monitoring data in dietary exposure analyses with the goal of generating more realistic Tier 3 dietary exposure estimates by using some new features of the version 7 DEEM™ software. Version 7 DEEM software now permits non-representative, stratified sampling of data to be incorporated into dietary risk assessments. Currently, the use of FDA surveillance monitoring data and its incorporation into Agency risk assessments relies on the professional judgement of the reviewer and depends on the degree of over-sampling of imported produce observed, the differences in residue concentrations between domestic and imported produce, and the sample size. If there are significant differences between domestic and import samples, either in terms of likelihood of detected residues, or residue levels themselves, then it would be desirable to "weight" the FDA data such that it better reflects the proportionate mix between domestic and foreign produce which the U.S. population consumes. Additional estimates of the percent of commodity imported as well as imported %CT from BEAD are also incorporated. For the endosulfan dietary risk assessments, both the non-weighted and weighted methodologies were used. The crops for which the Agency was able to incorporate the new procedures were dried beans, blueberries, cauliflower, cherries, fresh sweet corn, cucumbers, melons (except cantaloupe), fresh succulent peas, peppers, pineapples, plums, pumpkins, raspberries, and summer squash. The additional assessments included modifications to the above mentioned crops and these are the *only* differences between the weighted and non-weighted assessments. The acute and chronic dietary (food) risk estimates were below the Agency's level of concern for all population subgroups. Specifically, the acute dietary risk estimates at the 99.9th percentile for the general population were estimated to be 13% and 9% of the aPAD, without and with (wo/w) weighted FDA data, respectively, and the acute dietary risks for the most highly exposed population subgroup (children 1-6 years of age) were estimated to be 70% and 51% of the aPAD wo/w weighted FDA data, respectively. The chronic dietary risk estimates for the general population were estimated to be < 1% of the cPAD wo/w weighted FDA data, and the chronic dietary risks for the most highly exposed population subgroup (children 1-6 years of age) were 6% of the cPAD wo/w weighted FDA data.

Taking into account the supported uses proposed in this action, the Agency concluded with reasonable certainty that residues of endosulfan in drinking water would not likely result in a total (food + water) dietary risk above the Agency's level of concern. The Agency based this determination on a comparison of estimated concentrations of endosulfan in surface waters and ground waters to back-calculated "levels of comparison" for endosulfan in drinking water. The estimates of endosulfan in surface and ground waters were derived from water quality models that used conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water, and were supplemented with limited monitoring data. EFED estimated acute (peak) and chronic (average) surface water environmental effect concentrations (EECs) and a ground water EEC for endosulfan residues using screening-level models and limited monitoring data. Peak and chronic surface water EECs for the combined residues of á-endosulfan, â-endosulfan and endosulfan sulfate are 8.1 µg/L and 1.3 µg/L, respectively. The ground water EEC for the combined residues is estimated to be 0.012 µg/L. The available monitoring data indicate that 90th percentile values would not be expected to exceed peak EEC values. The Agency's Office of Water has not established a Maximum Contaminant Level (MCL) for endosulfan in water.

As mentioned above, the ETF is not supporting dust or smoke canister uses, or any uses of endosulfan in or around the home, around public buildings or recreational areas. Therefore, the Agency did not include the affected non-agricultural and residential uses in its revised risk assessment. However, labels exist that have not incorporated these changes and will need to be amended. Previous risk assessments showed unacceptable risks associated with smoke canister, home and recreational uses. In addition, the Agency is currently in the process of expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from sources other than residential uses, such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools. Modifications to this assessment shall be incorporated as updated guidance becomes available.

The occupational exposure assessment consisted of an analysis of the potential for dermal and inhalation exposure to occur in: 1) occupational pesticide handlers (includes mixers, loaders, and applicators); and 2) postapplication workers during harvesting or other activities. Surrogate-based exposure assessments for each scenario (including those that involve airblast application) were developed where appropriate data were available using the Pesticide Handlers Exposure Database (PHED) Version 1.1, and standard values.

There are agricultural and non-agricultural (e.g. ornamentals, rights-of-way) short-term dermal and inhalation occupational exposures to handlers that pose potential risks (Margins of Exposure < 100), even with maximum feasible mitigation measures. It is desirable that short-term occupational risks, expressed as MOEs, be above 100. MOEs below 100 are of concern. Dermal and inhalation risks for handlers were assessed separately since the end effects for the toxicological endpoints chosen for these exposures are dissimilar and Agency policy prevents aggregation of the risks (inhalation plus dermal) if the toxicological effects are not the same. Handler exposures to endosulfan are expected to be short-term only (1 - 30 days). Of the 21

identified occupational handler exposure scenarios, 13 of them are a risk of concern, at the highest level of mitigation for short-term dermal exposure. For short-term inhalation exposure, 4 of the 21 identified occupational handler exposure scenarios are a risk of concern, at the highest level of mitigation.

The Agency determined that there are several scenarios in which postapplication occupational exposure to endosulfan may occur. Most of these scenarios lead to dermal exposure of short- or intermediate-term (31 days to several months) duration. Postapplication exposures of long-term duration are not expected. Intermediate-term occupational MOEs $\geq$ 300 are not of concern. The dermal endpoints are based on the 21-dermal study in the rat for all exposure durations and for any duration longer than 30 days, an additional 3x safety factor was added to account for using a 21-day study for a duration of longer than 30 days. Hence, the target MOE = 300 for intermediate-term dermal exposures. For the purpose of conducting the occupational postapplication dermal exposure assessments, representative crop groups, and assumptions regarding application rates and dermal transfer coefficients were used. Many of the postapplication exposure scenarios lead to potential risks that are of concern. Current endosulfan labels list restricted-entry interval (REI) requirements that range from minimal reentry restrictions (sprays have dried, etc.), to a 24-hour REI with the following early entry personal protective equipment (PPE) required: coveralls, chemical resistant gloves, shoes, socks, and chemical resistant headgear for overhead exposures. For short-term postapplication exposures, the day after treatment with the emulsifiable concentrate (EC) formulation when the calculated MOE equals or exceeds the target MOE of 100 ranges from 2 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting, to 28 days for detasseling corn at an application rate of 1.5 lbs ai/acre. For the wettable powder (WP) formulation, the day after treatment when the calculated MOE $\geq$ 100 ranges from 8 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting, to 49 days for girdling grapes at an application rate of 1.5 lbs ai/acre. For intermediate-term postapplication exposures, the number of days after treatment with the EC when the estimated MOE is $\geq$ 300 ranges from 2 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting to 28 days for detasseling corn at an application rate of 1.5 lbs ai/acre. For the WP formulation, the day after treatment when the calculated MOE $\geq$ 300 ranges from 8 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting to 52 days for girdling grapes at an application rate of 1.5 lbs ai/acre. Thus, the current REI requirements do not appear to be sufficiently protective.

Several incidents of acute accidental human exposure to endosulfan have been reported. The clinical signs and symptoms observed in humans following acute accidental exposure to endosulfan are similar to those observed in acute toxicity studies in animals. In humans, acute toxicity caused by endosulfan is characterized by nervousness, agitation, tremors, convulsions, and death. In one incident, a 70 year old woman died about three hours after she swallowed "drops" of an endosulfan formulation. Prior to death the woman experienced vomiting, diarrhea, agitation, tonoclonic convulsions, dyspnea, cyanosis, and loss of consciousness. In another

incident, nine workers experienced at least one convulsion after bagging a 50% wettable powder formulation of endosulfan. Five of the men were said to be wearing a respirator and protective clothing at the time of exposure. Prodromal symptoms included malaise, vomiting, dizziness and confusion.

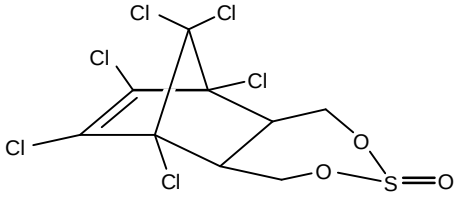
The aggregate risk assessment for endosulfan considers exposure from food, drinking water, and residential uses. Exposures to endosulfan from dietary (food and water) sources alone are not of concern. The Agency has concluded with reasonable certainty that no harm to any population will result from either acute or chronic dietary (food and water) exposure to endosulfan residues. Drinking water levels of comparison (DWLOCs) that correspond to potential acute and chronic consumption of water by the general population and specific population subgroups (i.e., infants, children, and females of child-bearing age) were compared to the EECs. The calculated DWLOCs for all populations are greater than the peak, chronic and ground water EECs. Therefore, when considered along with exposure from consumption of foods containing residues of endosulfan, potential drinking water exposures are not expected to result in aggregate risks of concern. As mentioned above, residential uses are not being supported for reregistration and were not included in this assessment.

In conclusion, there are no dietary risk concerns for endosulfan. There are however, occupational risk concerns, even with the highest feasible level of mitigation (PPE, engineering controls).

2.0 PHYSICOCHEMICAL PROPERTIES CHARACTERIZATION

Endosulfan is a polychlorinated, non-ionic tricylic hydrocarbon that contains a cyclic sulfite ester moiety. The fused tricylic ring structure makes possible the two isomers, á-endosulfan and â-endosulfan. [In some reference sources (e.g. USDA's Pesticide Data Program database) á-endosulfan is called "endosulfan I", and â-endosulfan is called "endosulfan II".] The general structure of endosulfan and the specific structures of its á- and â-isomers are shown below. Also shown is endosulfan sulfate, a plant, animal, and environmental metabolite of toxicological concern. The numbers in parentheses are the Chemical Abstracts Service registry numbers.

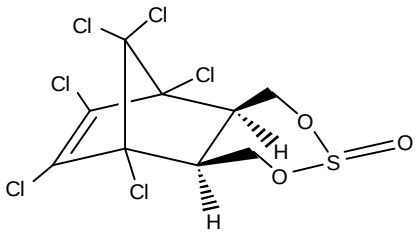
While often referred to generically as a "cyclodiene-type" insecticide, endosulfan contains only one double bond. Technical endosulfan (70% á- and 30% â-endosulfan) is a light to dark brown crystalline solid. Compared to most other discrete organic pesticides, endosulfan is relatively large in mass (molecular weight is 406.95 daltons). The melting point of the á-isomer ranges from 108-110^0 C and the melting point of the â-isomer is 208-210^0 C. The



endosulfan

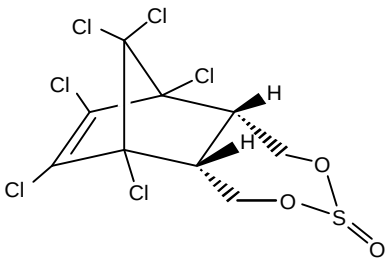
(115-29-7)

(stereochemistry unspecified)



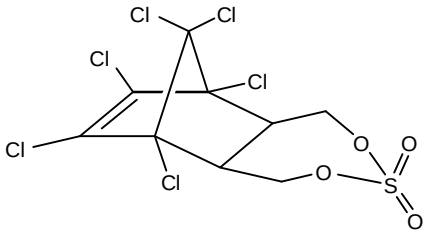
alpha-endosulfan

(959-98-8)



beta-endosulfan

(33213-65-9)



endosulfan sulfate

(1031-07-8)

Figure 1. Structures of: endosulfan (stereochemistry unspecified); alpha-endosulfan; beta-endosulfan; and endosulfan sulfate.

melting point of technical endosulfan ranges from 70 to 100^0 C. The vapor pressure of á-endosulfan is 3.0×10^{-6} mm Hg, â-endosulfan 7.2×10^{-7} mm Hg, and technical endosulfan 1×10^{-5} mm Hg at 25 ^{0}C. Technical endosulfan has a water solubility that varies from insoluble to ~0.33 mg/L at 25 ^{0}C, but appreciable lipophilicity (log P 4.445 to 5.689). See *Endosulfan, Product Chemistry Chapter for Reregistration Eligibility Decision*. Ken Dockter, December 18, 1998.

Hexachlorobenzene and pentachlorobenzene are present in technical endosulfan in very low concentrations. These substances are not formed during the manufacture of endosulfan, but are contaminants of the feedstocks used for the manufacture of endosulfan. The concentration of hexachlorobenzene in technical endosulfan ranges from <75 to 290 μg/kg and the concentration of pentachlorobenzene ranges from 1000 to 4900 μg/kg. The reaction conditions of the synthesis used to manufacture endosulfan are such that formation of chlorinated dioxins or dibenzofurans are not expected.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Except for the absence of subchronic neurotoxicity and developmental neurotoxicity studies, the toxicology database is sufficiently complete to for risk assessment purposes. Endosulfan is a chlorinated cyclodiene pesticide, and like other members of this chemical group, the predominant toxicological effect is over stimulation of the central nervous system [by inhibiting Ca^{2+}, Mg^{2+} - ATPase and antagonizing chloride ion transport in gamma-aminobutyric acid (GABA) receptors] with little or no peripheral component. Convulsions (seizures) are the most important symptoms of endosulfan toxicity. Characteristic clinical signs following acute exposure are indicative of central nervous system (CNS) disturbances or over stimulation and include, hyperactivity, incoordination, seizures, convulsions, and death. Although these effects were not generally observed at the Lowest Observable Adverse Effect Level (LOAEL), at higher doses, they were observed in the acute and subchronic toxicity studies and developmental studies in the rat and rabbit. In a chronic feeding study, dogs also exhibited central nervous system disturbances such as abnormal righting reflexes, tonic contractions, involuntary muscle movements, and pronounced sensitivity to noise and light.

Endosulfan is highly acutely toxic via the oral and inhalation routes of exposure, with LD_{50} and LC_{50} values of 30 mg/kg bw and $\leq$ 0.5 mg/L, respectively, placing it in Toxicity Category I. By the dermal route, however, endosulfan was less toxic, with an LD_{50} of 2000 mg/kg, (Toxicity Category III). Further, endosulfan is an eye irritant in rabbits (Toxicity Category I), but is not a dermal irritant or sensitizer.

The subchronic toxicity of endosulfan was evaluated in two 13-week feeding studies in the rat and mouse, two 21-day dermal toxicity studies in the rat, and one 21-day inhalation study, also in the rat. In general, females are more sensitive to the toxic effects than males. In the 13-week

feeding studies, anemia occurs (consisting of decreased hemoglobin and/or decreased mean red blood cell hemoglobin concentration) at the LOAEL and higher doses in both rats and mice. Treatment-related anemia, however, was not observed in any of the 21-day dermal or inhalation studies. In the dermal studies in rats increased mortality was observed at the LOAEL. In one of the dermal studies, other toxic effects at the LOAEL included increased incidence of liver abnormalities in males and females and increased absolute spleen weight in females. In the other 21-day dermal toxicity study, females had hypersalivation (CNS effect) at the LOAEL. In the 21-day inhalation toxicity study, the LOAEL was established by decreased body-weight gain and decreased leukocyte counts in the males and increased creatinine values in the females.

The chronic toxicity of endosulfan was evaluated in a combined two-year feeding/ carcinogenicity study in rats, a one-year feeding study in dogs, and an carcinogenicity study in mice. Chronic toxicological endpoints at the LOAEL included, in part, decreased body weight gain in male and female rats (♂2.9 & ♀3.8 mg/kg/d) and decreased body weight in male dogs (≈1.75 mg/kg/d). Additional effects at the LOAEL included neurological effects in female dogs, marked progressive glomerulonephrosis (kidney toxicity) in male and female rats and blood vessel aneurysms in males rats. Endosulfan did not exhibit any oncogenicity in rats or mice.

The developmental toxicity of endosulfan was evaluated in rats and rabbits. Maternal toxicity at the LOAEL included decreased body weights in rats and rabbits and increased incidence of clinical signs in rats (tonoclonic convulsions, increased salivation, mortality) and rabbits (convulsions, rapid breathing, salivation, hyperactivity, mortality). Developmental toxicity in the rat included a slight increase in the incidence of fragmented thoracic vertebral centra and a slight increase in the occurrence of microsomic fetuses. No developmental toxicity was observed in rabbits. There are no indicators of an increased quantitative sensitivity to the fetus in either the rat or rabbit study; the LOAELs for developmental toxicity were equal to or greater than the LOAELs for systemic maternal toxicity.

The reproductive toxicity of endosulfan was evaluated in a two-generation study in the rat. LOAELs for parental systemic and developmental toxicity were established at the highest dose tested. The LOAEL for parental systemic toxicity was based on decreased body weight and for developmental toxicity, increased pituitary and uterine weights. The increases in pituitary gland and uterine weights are suggestive of possible effects on hormonal metabolism and endocrine function. These effects also suggest a potential qualitative sensitivity of offspring to endosulfan exposure either in utero or during early development. The increased incidence of parathyroid hyperplasia in male rats in the carcinogenicity study and several open literature publications also suggest that endosulfan has hormonal effects.

Endosulfan was evaluated in an acute neurotoxicity screening battery in the rat and an acute delayed neurotoxicity study in the hen. The LOAEL in the rat study was based on behavioral disturbances such as increased incidences of stilted gait, hunched posture, irregular respiration, and decreased spontaneous activity in males and females; females also had increased incidence of straddled hindlimbs, panting, and bristled coat. The acute delayed neurotoxicity

study in the hen showed no evidence of progressive nerve damage in the brain, spinal cord and peripheral nerve.

Endosulfan was not oncogenic and did not show any mutagenic potential. There was no increase in the frequency of tumors in either the rat or mouse carcinogenicity studies. Endosulfan is classified as having no evidence of oncogenicity for humans by the Agency. The submitted mutagenicity studies have satisfied the data requirements for mutagenicity testing, and there is no concern for a mutagenic effect in somatic cells. In the *in vitro* or *in vivo* mutagenicity studies, both the mouse lymphoma forward mutation assay and the unscheduled DNA synthesis assay were negative.

Both hexachlorobenzene and pentachlorobenzene are considered by the Agency to be possible human carcinogens (B2 carcinogens). Agricultural use of endosulfan poses a potential source of human dietary exposure to hexachlorobenzene and pentachlorobenzene and, therewith, poses a potential source of cancer risk. Hexachlorobenzene itself was once registered in the United States as a pesticide active ingredient. The use of hexachlorobenzene in the United States as a pesticide active ingredient was canceled in 1984 (USEPA, 1985). In 1998 the Agency assessed the cancer risks posed by dietary exposure to hexachlorobenzene and pentachlorobenzene from the use of endosulfan and the other pesticide active ingredients mentioned above (*Assessment of the Dietary Cancer Risk of Hexachlorobenzene and Pentachlorobenzene as impurities in Chlorothalonil, PCNB, Picloram, and several other pesticides.* William Smith, February 26, 1998) and concluded that the cancer risk to humans from all pesticidal sources of dietary exposure to the combined residues of hexachlorobenzene and pentachlorobenzene was 1.81×10^{-6}. The Agency generally regards risk estimates that are greater than 1×10^{-6} to be risks of concern. While the estimated cancer risk posed by dietary exposure to hexachlorobenzene and pentachlorobenzene from use of pesticides that contain these substances is slightly greater than 1×10^{-6}, the Agency believes that its cancer risk estimate is an overestimate of actual cancer risk. This is largely because the cancer risk assessment was based on several worst-case assumptions regarding the concentrations of hexachlorobenzene and pentachlorobenzene in the pesticide active ingredients and in foods. Experimental data show that the actual concentrations of hexachlorobenzene and pentachlorobenzene in the pesticide active ingredients are much lower than the concentrations used in the dietary exposure calculations.

Studies with radiolabeled endosulfan evaluated the metabolism in the rat and mouse and dermal absorption in the rat. Endosulfan was found to be rapidly metabolized into mainly water-soluble compounds and eliminated with very little absorption in the gastrointestinal tract. The primary metabolites include endosulfan sulfate, endosulfan diol, endosulfan ether, endosulfan alpha-hydroxy ether, and endosulfan lactone. The metabolites accumulated in tissues, especially in the kidney and liver. Following dietary exposure to endosulfan, a large amount of endosulfan sulfate was recovered in the liver, small intestine and visceral fat with a trace of this metabolite in the muscle. Dermal absorption studies in male and female rats showed that endosulfan is slowly absorbed through the skin and is slowly excreted, which suggests that endosulfan bioaccumulates in the body. A dermal absorption factor of 45% was used for assessment of occupational

exposure.

There was no evidence of increased susceptibility in rat and rabbit fetuses following *in utero* exposures in the submitted prenatal toxicity studies in rats and rabbits or increased quantitative sensitivity in the offsprings as compared to parental animal following pre/post natal exposure in the two generation reproduction study. Effects noted in the offspring, such as increased uterine and pituitary gland weights, however, suggest a potential qualitative sensitivity of animals exposed to endosulfan in utero or during early development.

The open literature suggests that endosulfan may affect normal hormone metabolism and endocrine function. In studies submitted to the Agency, treatment-related effects were seen in the two-generation reproduction study in rats, characterized as increases in the pituitary gland weights and as increased incidences of parathyroid hyperplasia in male rats in the carcinogenicity study. See *Endosulfan 079401: Toxicology Chapter for the Reregistration Eligibility Document*, Nicole Paquette/David Liem, November 22, 1999.

3.2 Pharmacokinetics

Results from toxicity studies, metabolism studies, and dermal absorption studies indicate that endosulfan is absorbed following oral, inhalation, or dermal exposure. Absorption from the skin appears to be slow and incomplete. In a study involving rats, radiolabeled-endosulfan was applied dermally at doses of 0.1, 1, and 10 mg/kg for ten hours, after which the skin was washed with soap and rinsed with water. The percent of dose absorbed at 24 hours post-dosing were 22.1, 16.1 and 3.8%, and at 168 hours were 44.8, 46.4 and 20.3% for the 0.1, 1, and 10 mg/kg dose groups, respectively. The percentages of the doses remaining on/in the skins at 168 hours were 41.4, 56.2 and 72.8% for the 0.1, 1, and 10 mg/kg dose groups, respectively.

Following absorption from the oral or dermal exposure routes endosulfan is partially metabolized, primarily to endosulfan sulfate. Minor metabolites include endosulfan diol, endosulfan ether, endosulfan á-hydroxy ether, and endosulfan lactone. None of the minor metabolites of endosulfan are believed to be of toxicological concern. Endosulfan and its metabolites partition and accumulate predominately in the kidney and liver. Following dietary exposure to endosulfan, a large amount of endosulfan sulfate is recovered in the liver, small intestine and visceral fat, and only a trace amount is recovered in muscle tissue. Endosulfan and its metabolites are excreted in both the urine and feces, the latter being the predominant route of excretion. Most of an absorbed dose of endosulfan is excreted within a few days to a few weeks, depending upon dose and route of exposure.

3.3 Acute Toxicity

Endosulfan is highly toxic following acute oral exposure and moderately toxic following acute inhalation exposure. In rats, oral median lethal doses (LD_{50} values) are 82 mg/kg (males) and 30 mg/kg (females). Medium lethal concentrations (LC_{50} values) in rats following acute

inhalation exposure range from 0.16 to 0.5 mg/L. Endosulfan is considerably less lethal, however, following acute dermal exposure (LD_{50} is 2 g/kg). Endosulfan is an eye irritant in rabbits (Toxicity Category I) but is not a dermal irritant or sensitizer.

Table 1. Summary of Results from Acute Toxicity Assays of Endosulfan.

Guideline#	Study Type	MRID	Results	Toxicity Category
870.1100	Acute Oral (50% wettable powder)	41183502	LD_{50} = 82 mg/kg in ♂ LD_{50} = 30 mg/kg in ♀	I
870.1200	Acute Dermal (50% wettable powder)	41183503	LD_{50} = 2000 mg/kg	III
870.1300	Acute Inhalation 50% wettable powder)	41183504	LC_{50} = 0.16-0.5 mg/L	II
870.2400	Primary Eye Irritation 50% wettable powder)	41183505	Eye irritant (Residual opacity at day 13)	I
870.2500	Primary Skin Irritation 50% wettable powder)	41183506	Non-irritant	IV
870.2600	Dermal Sensitization	41183507	Not a dermal sensitizer	NA

3.4 Subchronic and Chronic Toxicity

The potential for endosulfan to cause toxicity following subchronic exposure was evaluated in several assays that included: two separate 13-week feeding studies in rats and mice, two 21-day dermal toxicity studies in rats, and one 21-day inhalation study in rats. In the 13-week feeding studies, treatment-related hematological effects (consisting of decreased hemoglobin and/or decreased mean red blood cell hemoglobin concentration) were noted in both species.

Treatment related effects observed in the dermal toxicity studies involving application of endosulfan technical to the skins of rats included increased mortality in female rats, decreased body weights in male rats, increases in reticulocyte counts in both sexes, decreased plasma cholinesterase activity in both sexes, hypersalivation (females), tonic convulsions (females) and tonoclonic convulsions (males), hepatotoxicity in males and females, and increased absolute spleen weight in females. The treatment-related hematological effects observed in the subchronic dietary study were not observed in the 21-day dermal study. In the 21-day inhalation toxicity study conducted in male and female rats, toxicological effects believed to be treatment related were decreased body-weight gain and leukocyte counts (males) and increased creatinine values (females).

The potential for endosulfan to cause toxicity following chronic exposure was evaluated from the results of three separate studies that included: a combined two-year feeding/ oncogenicity study in rats; a one-year feeding study in dogs; and an oncogenicity study in mice. Some of the noteworthy treatment-related effects observed in these studies were: 1) decreased body weight gain (observed in male and female rats, and male dogs); 2) neurological effects

(observed in female dogs as extreme sensitivity to noise and optical stimuli, tonic contractions, and in male dogs as a loss of righting reflex and placing reaction); 3) marked progressive glomerulonephrosis (observed in male and female rats); 4) blood vessel aneurysms (observed in male rats), and 5) increased mortality (observed in female mice).

Endosulfan is neither oncogenic nor mutagenic. The oncogenicity studies conducted in rats and mice do not indicate that exposure to endosulfan will result in an increased incidence of neoplastic lesions. In *in vitro* or *in vivo* mutagenicity studies, both the mouse lymphoma forward mutation assay and the unscheduled DNA synthesis assay were negative.

The neurotoxic properties of endosulfan were characterized primarily from results of two studies: a screening battery study conducted in rats and a 42-day delayed neurotoxicity study conducted in hens. In the rat study, endosulfan was administered as a single (acute) dose, and neurotoxic signs were observed in both male and female rats. For male and female rats, clinical observations indicative of neurotoxicity included: increased incidences of stilted gait; squatting posture; irregular respiration; and decreased spontaneous activity. Female animals also exhibited an increased incidence of straddled hindlimbs, panting and bristled coat. In the delayed neurotoxicity study no evidence of progressive nerve damage in the brains, spinal cords, or peripheral nerves of treated Leghorn hens was identified.

In addition to the studies described above, the neurotoxicity of endosulfan was evaluated from results of other toxicity studies submitted under OPPTS guidelines. Results from some of these studies indicate that endosulfan causes neurotoxicity. In a subchronic (13-week) feeding study, plasma cholinesterase activity was reduced by 40% at week 13 in female rats administered endosulfan at 360 mg/kg/day. In a separate subchronic toxicity study in which endosulfan was administered dermally to rats, decreased plasma cholinesterase activity and tonoclonic convulsions were seen in females. In a chronic study in which endosulfan was administered to dogs via the diet, signs indicative of neurological effects were noted and included loss or weakening of righting reactions, and tonic contractions of the abdominal and masticatory muscles. In a developmental toxicity study conducted in rats, dams dosed at 6 mg/kg exhibited tonoclonic seizures, increased salivation, and hyperactivity. In a developmental toxicity study conducted in rabbits, does dosed at 1.8 mg/kg exhibited rapid breathing, increased salivation, hyperactivity and tonoclonic convulsions.

The potential for endosulfan to cause developmental toxicity was evaluated from the results of studies conducted in pregnant rats and rabbits under OPPTS guidelines, and from a published study involving neonatal rats (Lakshmana and Raju, 1994). In the studies conducted under OPPTS guidelines, pregnant animals were exposed to endosulfan. Results from the OPPTS guideline studies indicate that there is no increased or special fetal sensitivity to the toxicity of endosulfan. Treatment-related developmental toxicity was only noted in the rat study, and only occurred at the dose (highest dose tested) that also caused maternal toxicity. The developmental toxicity was characterized by a slight increase in the incidence of fragmented thoracic vertebral centra and a slight increase in the occurrence of fetuses weighing less than 3 grams. Results from

the study published by Lakshmana and Raju (1994) suggest that neonates could have special or increased sensitivity to the effects of endosulfan. In this study rat pups of both sexes were administered endosulfan via gastric intubation at 6 mg/kg/day from post-natal days 2-25. Levels of acetyl cholinesterase, noradrenaline, dopamine and serotonin were assayed in olfactory bulb, hippocampus, visual cortex, brainstem and cerebellum. Performance in operant conditioning for solid food reward was assessed in 25-day-old rats. Compared to control animals, noradrenaline levels in treated animals were increased in the olfactory bulb, brainstem, hippocampus and cerebellum at 25 days of age. Dopamine levels were decreased in the hippocampus at both 10 and 25 days. Serotonin levels were increased in the olfactory bulb, hippocampus, visual cortex and brainstem at 10 days of age, but were decreased in the brainstem and cerebellum at 25 days of age. The activity of acetyl cholinesterase was not different from the control groups in any of the regions studied. These changes in the concentrations of noradrenaline, dopamine, and serotonin in the brains of treated neonates were accompanied by deficits in acquisition as well as retention of memory.

The potential for endosulfan to cause reproductive toxicity was evaluated from results of an OPPTS two-generation guideline study conducted in rats. In this study, an initial parent (F_0) generation of rats were exposed to endosulfan (97% ai) via the diet during premating and through gestation and lactation periods, at dose levels of: 0, 0.20, 1.00, and 4.99 mg/kg/day in males; and 0, 0.24, 1.23, and 6.18 mg/kg/day in females. No reproductive toxicity was noted. Pregnancy rate, gestation times, the ability to rear young to weaning, and pre-coital time were comparable among the groups at both matings in both the F_0 and F_1 generations. Some effects indicative of developmental toxicity were noted, but only at doses (the highest doses tested) that caused parental toxicity. These effects include: increased pituitary weights in high-dose female pups of the first mating of the F_0 generation; and increased uterine weights in high-dose female pups of the first mating of the F_1b generation. The parental effects that occurred at the same or lower dose levels include the following: increased heart weight at the mid- and high-dose levels and increased liver and kidney weights at the high-dose level (F_0 males); increased brain and liver weights at the high-dose level (F_0 females).

Table 2. Subchronic, Chronic, and Other Toxicity

Guideline #/Study Type	MRID # /Year/Classification/Doses	Results
870.3100 13-week subchronic feeding study in rats (97.2%)	00145668 (1985) Acceptable/Guideline 0,0.5, 1.5, 3.0, and18 mg/kg/d	LOAEL=1.5 mg/kg/d based on kidney abnormalities and increased spleen weight in male rats. NOAEL=0.5 mg/kg/d
870.3100 13-week subchronic feeding study in mice (97.2%)	00147182 (1984) Acceptable/Guideline 0, 0.24, 0.74, 2.13, and 7.3 mg/kg/d for males. 0, 0.27, 0.80, 2.39, and 7.52 mg/kg/d for females.	LOAEL=7.3 mg/kg/d based on high incidences of mortality in both males and females. NOAEL=2.1 mg/kg/d in males.

870.3200 30-day subchronic dermal toxicity study in rats (49.5%)	41048506 (1987) Acceptable/Guideline 0, 160, and 640 mg/kg/d for males. 0, 80, and 160 mg/kg/d in females.	Systemic LOAEL=640 mg/kg/d in males based on body weight. LOAEL=80 mg/kg/d in females based on mortality and decreased plasma ChE activity. NOAEL=160 and 40 mg/kg/d in males and females, respectively.
870.3200 21-day dermal toxicity study in rats (97.2%)	146841 (1985) & 147744 (1985). Acceptable/Guideline 0, 12, 48, 96, and 192 mg/kg/d for males. 0,3, 6, 12, and 48 mg/kg/d for females. 21 applications over 30 days.	Systemic LOAEL=192 mg/kg/d in males based on increased mortality and plasma ChE inhibition. NOAEL=96 mg/kg/d. Systemic LOAEL=48 mg/kg/d for females based on mortality and increased incidence of neurotoxic clinical signs. NOAEL=12 mg/kg/d.
870.3200 21-day dermal toxicity study in rats (97.2% w/w)	257684 & 257685 (1985) Acceptable/Guideline 0, 1, 3, 9, and 27 mg/kg/d for males and females, and 6 males only at 81 mg/kg/d, for 21 applications over 30 days.	Systemic NOAEL=3 mg/kg/d. LOAEL=9 mg/kg/d based on increased mortality in males, and increased liver abnormalities (enlargement of parenchymal cells, loss of cytoplasmic basophilia and isolated cell necrosis and frequent mitosis) in both sexes.
870.3455 21-day inhalation study in rats (97.2%)	41667501 (1990) supplemental to 00147183 (1984) Acceptable/Guideline 0, 0.0005, 0.0010, and 0.0020 mg/L air (0.097, 0.194, 0.387 mg/kg/d) both sexes nose-only for 6 hrs/d for 21 exposures over 29 days.	NOAEL=0.001 ai/L (0.194 mg/kg/d) and LOAEL= 0.002 ai/L (0.387 mg/kg/d) based on decreased body weight gain and decreased leukocyte counts in males and increased creatinine values in females.
870.4100 1-year chronic toxicity feeding study in dogs (96.5%)	41099501 (1989) Acceptable/Guideline 0, 3, 10, 30, and 30/45/60 ppm (0, 0.65, 1.75, 0.65-1.30 mg/kg/d for males and 0, 0.57, 1.75, and 0.65-1.30 mg/kg/d for females).	NOAEL= 10 ppm (0.65 and 0.57 mg/kg/d in males and females, respectively) and LOAEL= 30 ppm (≈1.75 mg/kg/d) based on decreased body weight gain in males and increased incidences of neurologic findings in males and females (loss or weakening of placing and righting reactions, tonic contractions of abdominal muscle and masticatory muscles a few hours after feeding).
870.4300 Chronic/Carcinogenic Feeding Study in Rats (97.1%)	41099502 (1989) Acceptable/Guideline 0, 3, 7.5, 15, and 75 ppm (0, 0.1, 0.3, 0.6, 2.9 mg/kg/d for males and 0, 0.1, 0.4, 0.7, and 3.8 mg/kg/d for females) for 104 weeks	Systemic NOAEL= 15 ppm (0.6 and 0.7 mg/kg/d for males and females, respectively) and LOAEL= 75 ppm (2.9 and 3.8 mg/kg/d for males and females, respectively) based on decreased body weight gain in males and females, enlarged kidneys in females, and increased incidences of marked progressive glomerulonephrosis in males and females, and blood vessel aneurysms in males. Dosing was considered adequate.

870.4200 Chronic/Carcinogenic Feeding Study in Mice (97.9%)	40792401 (1988) Acceptable/Guideline for oncogenicity but, not acceptable for a combined chronic/oncogenicity study in mice because some clinical chemistry parameters were not evaluated. 0, 2, 6 and 18 ppm (0, 0.3, 0.9 and 2.6 mg/kg/day) for 24 months	Systemic NOAEL= 6 ppm (0.9 mg/kg/day), and LOAEL = 18 ppm (2.65 mg/kg/day), based on increased incidences of mortality in females. At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate.
870.3700 Developmental Toxicity in Rats (97.3%)	43129101 (1993) Acceptable/Guideline 0 (sesame oil), 0.7, 2.0, and 6.0 mg/kg/d from days 7 through 16 of gestation by gavage. This study was a repeat study for an unacceptable developmental toxicity study (ACC# 243707).	Maternal toxicity NOAEL= 2.0 mg/kg/d and LOAEL= 6.0 mg/kg/d based on 80 % mortality, tonoclonic convulsions, increased salivation, and decreased body weight gains and food consumption. Developmental toxicity NOAEL= 2.0 mg/kg/d and LOAEL= 6.0 mg/kg/d based on a slight increase in the incidence of fragmented thoracic vertebral centra and a slight increase in the occurrence of fetuses/litter weighing less than 3 grams.
870.3700 Developmental Toxicity in Rabbits (97.3%)	00094837 (1981) Acceptable/Guideline 0, 0.3, 0.7, and 1.8 mg/kg/d from days 6 through 28 of gestation by gavage	Maternal NOAEL= 0.7 mg/kg/d and LOAEL= 1.8 mg/kg/d based on decreased body weight, as well as increased incidences of deaths, convulsions, rapid breathing, salivation and hyperactivity. Developmental NOAEL= 1.8 mg/kg/d, the highest dose tested
870.3800 2-Generation Reproductive Toxicity in Rats (97%)	00148264 (1984) Acceptable/Guideline 0, 3, 15, and 75 ppm (0, 0.2, 1.0, and 5.0 mg/kg/d in males and 0, 0.2, 1.2, and 6.2 mg/kg/d in females) in the diet for two generations	Parental toxicity NOAEL= 15 ppm (1.2 mg/kg/d) and LOAEL= 75 ppm (6.2 mg/kg/d) based on decreased body weight. Reproductive effects NOAEL= 75 ppm (6.2 mg/kg/d), the highest dose tested. Developmental toxicity NOAEL= 15 ppm (1.2 mg/kg/d) and LOAEL= 75 ppm (6.2 mg/kg/d), based on increased pituitary and uterine weights.
870.6200 Acute Neurotoxicity screen in rats (98.6%)	44403101 (1997) Acceptable/Guideline One control group was assigned to males, dosed by gavage at 25, 50 and 100 mg/kg and females dosed at 3, 6 and 12 mg/kg. The other control group was assigned to males dosed at 6.25 and 12.5 mg/kg and females at 0.75 and 1.5 mg/kg.	NOAEL= 12.5 mg/kg for males, 1.5 mg/kg for females. LOAEL= 25 mg/kg for males based on increased incidences of stilted gait, squatting posture, and irregular respiration, as well as decreased spontaneous activity. LOAEL= 3 mg/kg for females based on an increased incidence of stilted gait, squatting posture, straddled hindlimbs, irregular respirations, panting and bristled coat and decreased spontaneous activity.
870.5300 Chromosome Aberrations in mice (97.2%)	00148266 (1984) Acceptable Six doses ranging from 6.25- 50 µg/ml w/o S9 activation, seven doses from 6.25-100 µg/ml with S9 activation induced a significant increase in mutations at the thymidine kinase (TK) locus in L5178Y mouse lymphoma.	Non-mutagenic in the mouse lymphoma forward mutation assay.

870.5550 Unscheduled DNA Synthesis in rat (97.2%)	00148265 (1984) Acceptable Cytotoxicity and UDS assay were performed in parallel. Fifteen test concentrations ranging from 1020- 0.102 µg/ml.	Inactive in primary rat hepatocyte unscheduled DNA synthesis (UDS) assay.
870.7485 Metabolism in Rats	050037030 (1978)	Metabolites accumulated in tissues, especially in the kidney and liver. Metabolites include endosulfan sulfate, endosulfan diol, endosulfan ether, endosulfan alpha-hydroxy ether, and endosulfan lactone.
870.7485 Metabolism in Mice	00004257 (1966)	Large amount of endosulfan sulfate was recovered in the liver, small intestine and visceral fat with a trace of this metabolite in the muscle.
870.7600 Dermal Penetration in Rats (94.6%)	40223601 (1986) Acceptable Males treated topically with radiolabeled suspension at nominal doses of 0.1, 1.0, and 10 mg/kg and exposed for 0.5, 1, 2, 4, 10 and 24 hrs.	% doses absorbed over 24-hour period were 2.2-21.6, 0.32-21.52, and 0.08-8.38 for the 0.1, 1.0, and 10 mg/kg dose groups, respectively. % doses remaining in/on the skin after soap and water washes over a 24-hour period were 62.1-56.5, 78.1-57.7, and 80.2-66.7 for the 0.1, 1, and 10 mg/kg dose groups, respectively. Significant portions of the dose remained on the skin. At 24-hour interval, endosulfan bioaccumulated in the body.
870.7600 Dermal Absorption in Rats (94.6%)	41048504 (1988) Acceptable Females treated topically with radiolabel at nominal doses of 0.1, 1, and 10 mg/kg (1.9, 21.9, and 231.4 mg/cm^2)	% doses absorbed at 24 hours were 22.1, 16.1 and 3.8% and at 168 hours were 44.8, 46.4 and 20.3% for the 0.1, 1, and 10 mg/kg dose groups, respectively. % doses remaining on/in skin at 168 hours were 41.4, 56.2 and 72.8% for the 0.1, 1, and 10 mg/kg dose groups, respectively. Showed that endosulfan bioaccumulated in the body. Dermal absorption factor of 45 % at 168 hours post exposure.

3.5 FQPA Considerations

The Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for indications of increased susceptibility of rats and rabbits to *in utero* and/or postnatal exposure to endosulfan. Although developmental toxicity was only seen at or above parentally toxic doses, there were treatment-related clinical signs of neurotoxicity following oral exposures in the rat, rabbit, and dog, and via the dermal route in rats. To fully assess the neurotoxic potential of endosulfan, acute and subchronic neurotoxicity studies in the rat were requested by the Agency. The acute neurotoxicity study was reviewed and found to be acceptable/guideline. The subchronic neurotoxicity study has not been received by the Agency and remains a data gap. Based on this data gap, the HIARC recommended that the requirement for a developmental neurotoxicity study be placed on reserve pending receipt and favorable

review of the subchronic neurotoxicity study. Subsequently, the FQPA Safety Factor Committee reviewed the hazard and exposure data for endosulfan (*Endosulfan - Report of the FQPA Safety Factor Committee,* Brenda Tarplee, November 20, 1998) and concluded that a developmental neurotoxicity study in rats should be requested now for endosulfan due to concern by the Committee for: 1) fetal effects reported in the open literature (Lakshmana and Raju 1994. Toxicology 91(2): 139-150); 2) the severity of effects seen in female offspring of the F_0 generation (increased pituitary) and F_1b generation (increased uterine weights) at the high-dose when compared to the toxicity observed in parental animals at this dose in the two-generation reproduction study in rats; and 3) the subchronic neurotoxicity study will only address the neuropathological concerns resulting from exposure to endosulfan. A developmental neurotoxicity study will provide the critical data needed to demonstrate the toxic effects of endosulfan on the developing fetal nervous system. Note: The protocols for the subchronic neurotoxicity and developmental neurotoxicity studies have been received and reviewed (D259978). The Agency is still awaiting the studies themselves.

The Committee concluded that the FQPA safety factor is required based on the uncertainty associated with the data gap (subchronic neurotoxicity and developmental neurotoxicity studies are requested), but can be reduced to 3x because: 1) there is no evidence of increased susceptibility in any submitted study; 2) the severity of the fetal effects in the reproductive toxicity study were not consistent between generations and the target organ toxicity seen in this study was not seen in any other study; and 3) reliable data and conservative assumptions were used to assess the potential dietary (food and water) exposure to this chemical.

The Committee determined that the FQPA safety factor of 3x is applicable for the following population subgroups:

Acute and Chronic Dietary Assessment: All populations which include infants and children. The FQPA [3x] factor is appropriate for these populations due to the uncertainty regarding the effects on the developing fetal nervous system (data gap).

Residential (Short-, Intermediate- and/or Long-Term) Assessment(s): All populations which include infants and children. The FQPA [3x] factor is appropriate for these populations since the potential for residential exposure to infants and children resulting from the use of endosulfan currently exists and there is uncertainty regarding the effects on the developing fetal nervous system after such exposure. Note: The ETF is not supporting residential uses and requested a residential use deletion for endosulfan. A 6F Notice was issued to this effect and no dissenting comments were received. Therefore, residential uses were not assessed.

3.6 Dose Selection

Due to the availability/submission of acceptable/guideline oral, dermal, and inhalation studies using endosulfan, the dietary, occupational, and residential risk assessments were conducted using route-specific endpoints. The acute dietary endpoint is based primarily on

neurotoxicity. The neurotoxicity is believed to result from over-stimulation of the central nervous system. Characteristic clinical signs of endosulfan-induced neurotoxicity include hyperactivity, tonic contractions, involuntary muscle movements, pronounced sensitivity to noise and light, incoordination, seizures, and convulsions. These clinical signs are observed in humans accidentally exposed to endosulfan, and in animal studies of varying treatment durations following different routes of exposure and in different animal species. The chronic dietary, and short-, intermediate-, and long-term dermal and inhalation endpoints are based on the toxic effects observed in animals following subchronic or chronic exposure , and include: neurotoxicity, hematological effects, and nephrotoxicity. In some animal studies endosulfan inhibited plasma cholinesterase at the highest doses tested. Endosulfan is not a dermal sensitizer, nor is it mutagenic or oncogenic.

3.6.1 Acute Reference Dose (RfD)

In an acute neurotoxicity study (MRID#44403101), male and female Wistar rats (10/sex/dose) were fasted overnight and then orally gavaged once with endosulfan (98.6%) suspended in 2% starch mucilage at a constant volume of 10 ml/kg body weights. Two separate control groups of 10 rats/sex were used in the study. One control group was assigned to males, dosed at 0 (vehicle), 25, 50 and 100 mg/kg and females dosed at 0 (vehicle), 3, 6 and 12 mg/kg. The other control group was assigned to males dosed at 0, 6.25 and 12.5 mg/kg and females at 0, 0.75 and 1.5 mg/kg. Rats were observed for 15 days and survivors were sacrificed at week three. The animals were evaluated for neurobehavioral effects (FOB and motor activity) on day 7 prior to dosing, and days 1 (within 8 hours after dosing), 8 and 15 of post-dosing. Neuropathological examinations were carried out at terminal sacrifice (at week 3) on ten rats/sex of controls and four 100 mg/kg male rats and five 12 mg/kg female rats.

Treatment-related clinical signs were noted within 8 hours after dosing on day one (peak-time of effects) in males at 50 and 100 mg/kg and females dosed at 6 and 12 mg/kg. These symptoms were not observed after day 2 in all survivors. Clinical signs noted included tonoclonic convulsions, decreased spontaneous activities, stilted gait, stupor, prone position, squatting posture, straddled hindlimbs, bristle coat, palpebral fissure narrowing, and irregular respiration and panting in males dosed at 50 and 100 mg/kg and females dosed at 6 and 12 mg/kg. In addition, increased incidences of the following signs; stilted gait, squatting posture, irregular respiration and decreased spontaneous activities in males dosed at 25 mg/kg; increased incidences of squatting posture, straddled hindlimbs, decreased spontaneous activities, bristle coat, irregular respiration and panting were also noted in females dosed at 3 mg/kg/day. Animals with “drawn in flanks” were only noted in females dosed at 3, 6, 12 mg/kg. Tremors were noted in three and four females dosed at 6 mg/kg and 12 mg/kg, respectively and in four males dosed at 50 mg/kg. Salivation was noted in one male dosed at 100 mg/kg, and in one female each dosed at 6 and 12 mg/kg. According to the study, the clinical effects observed were due to interaction of endosulfan with the brain gamma amino-butyric acid (GABA) receptors. No compound-related effects on motor activity were noted for rats that survived. No treatment-related effects were seen on: the rearing frequency, fore and hind-limb grip strength, and on landing foot-spread; body weight and

food consumption; organ weight; gross pathology; or histo(neuro) pathology. The NOAEL was 12.5 mg/kg for males and 1.5 mg/kg for females. The LOAEL was 25 mg/kg for males based increased incidences of stilted gait, squatting posture, and irregular respiration, as well as decreased spontaneous activity. The LOAEL was 3 mg/kg for females, based on an increased incidence of stilted gait, squatting posture, straddled hindlimbs, irregular respirations, panting and bristled coat and decreased spontaneous activity.

The dose and endpoint for establishing the RfD is the NOAEL= 1.5 mg/kg based on increased incidences of convulsions seen within 8 hours after dosing in females at 3 mg/kg. Though, the database included a lower NOAEL (maternal) of 0.7 mg/kg/day in the rabbit developmental toxicity study (MRID# 00094837), based on salivation, convulsions, rapid breathing, and hyperactivity seen at 1.8 mg/kg/day. The Committee, however, decided not to use this NOAEL for this (acute) scenario because the clinical signs in the dams were seen on day 10 of gestation (i.e., after 4 treatments) whereas in the acute neurotoxicity study, convulsions were seen 8 hours after a single oral dose, thus making this endpoint more appropriate for this risk assessment. An uncertainty factor of 100 was applied to account for inter-species variation (10x) and for intra-species extrapolation (10x).

Acute RfD: 1.5 mg/kg ÷ 100 (UF) = 0.015 mg/kg

Acute PAD (aPAD) for Infants, Children, and Females 13-50 years: 0.015 ÷ 3 (FQPA) = 0.005 mg/kg

aPAD for General Population: 0.015 ÷ 1 (FQPA) = 0.015 mg/kg

3.6.2 Chronic RfD

In a combined chronic/oncogenicity study (MRID# 41099502), groups of 50 Sprague-Dawley rats/sex/group were fed (in the diet) with technical endosulfan (97.1% ai) at 0, 3.0, 7.5, 15.0, and 75.0 ppm (≈ 0, 0.1, 0.3, 0.6, and 2.9 mg/kg/day for males and 0, 0.1, 0.4, 0.7, and 3.8 mg/kg/day for females) for 104 weeks. A satellite group of twenty rats/sex was dosed in a similar fashion and was used for hematology and clinical chemistry evaluations. No treatment-related effects on clinical signs, mortality, food consumption and urinalysis were observed. Mean body weights of the males and females dosed at 75.0 ppm were statistically significantly decreased ($p<0.01$; 17.6%) as compared to their respective controls. Grossly, enlarged kidneys were noted in females in the satellite group dosed at 75.0 ppm (8/20 *versu*s 2/20 in the controls).

No treatment-related changes were noted in the clinical chemistry and hematology parameters evaluated. Marginal decreases of leukocyte (at week 26) and lymphocyte counts (at weeks 26 and 52) were noted in the males dosed at 75.0 ppm. At week 13, RBC counts and MCV values were decreased in all treated females as compared to the controls. Since dose related trends were not evident and since no changes were noted at other intervals, these changes were not judged to be related to treatment. Increased incidences of blood vessel aneurysms (18/70 *versus* 10/70 in controls) and enlarged lumbar lymph nodes (19/70 *versus* 14/70 in

controls) were noted in the male rats dosed at 75.0 ppm as compared to the controls. Increased incidences of enlarged kidneys were seen in females dosed at 75 ppm (30/70 *versus 2*1/70 in controls) as compared to the controls. Other organ weights were not affected by dosing. Although slightly decreased testes weights were observed in males dosed at 15 and 75 ppm, these changes were not considered toxicologically significant. Histopathologically, increased incidences of blood vessel aneurysms (18/70 *versus* 9/70 in controls) were noted in male rats dosed at 75.0 ppm. Also, a significant increased incidence of marked progressive glomerulonephrosis in the kidneys was seen in male (30/70 *versus* 20/70 in controls) and in female (8/70 *versus* 1/70 in controls) rats dosed at 75.0 ppm. The incidence of the glomerulonephrosis in the kidneys in the high-dose males (43%) was higher than that observed in the historical controls (reported at 19.7%). These data were re-evaluated because of some concerns expressed by one member of the RfD/RfC Work Group (Memorandum: L. Taylor to G. Ghali, March 19, 1993). It was stated in this memo that the increase in the severity of progressive glomerulonephrosis in rats of both sexes at the high-dose level was regarded as an adverse effect and that the spontaneously occurring renal disease was exacerbated by exposure to the test material. No treatment-related neoplastic lesions were evident in this study. A slight increased incidence of pituitary adenoma in males and females dosed at 75 ppm, and fibroma/ adenoma of the mammary glands in females dosed at 75 ppm, was not judged to be related to treatment, because dose-related trends were not evident The doses used in this study appear to be adequate to test the carcinogenic potential of the test compound, as evidenced by the compound-related systemic effects noted above. Based on the results of this study, the systemic NOAEL is 15.0 ppm (0.6 and 0.7 mg/kg/day for males and females, respectively) and the systemic LOAEL is 75.0 ppm (2.9 and 3.8 mg/kg /day for males and females, respectively) based on decreased body weight gain in male and female rats, enlarged kidneys and increased incidences of marked progressive glomerulonephrosis and blood vessel aneurysms in males.

The dose and endpoint for the chronic RfD is the NOAEL= 0.6 mg/kg/day. The LOAEL= 2.9 mg/kg/day, based on reduced body weight gain, enlarged kidneys and increased incidences of marked progressive glomerulonephrosis in males and females, and blood vessel aneurysms in kidneys of male rats. The RfD/Peer Review considered the chronic toxicity study in dogs (MRID#41099501) with a NOAEL of 0.65 mg/kg/day to be a co-critical study. In this dog study, the LOAEL of 1.75 mg/kg/day was based on decreased body weight gain in males and increased incidences of neurologic findings in males and females (loss or weakening of placing and righting reactions, tonic contractions of abdominal muscle and masticatory muscles a few hours after feeding. The HIARC concurred with the conclusions reached by the RfD/Peer Review Committee with regard to the study, dose and endpoint used in establishing the RfD. An uncertainty factor of 100 was applied to account for inter-species variation (10x) and for intra-species extrapolation (10x).

Chronic RfD: 0.6 mg/kg ÷ 100 (UF) = 0.006 mg/kg/day

Chronic PAD (cPAD) for Infants, Children, and Females 13-15 years: 0.006 ÷ 3 (FQPA) = 0.002 mg/kg/day

cPAD for General Population: 0.006 ÷ 1 (FQPA) = 0.006 mg/kg/day

3.6.3 Dermal Absorption

Two dermal absorption studies were available. In one dermal absorption study (MRID #40223601), three groups of 24 male Crl: CD(SD) Br rats/group were dosed topically with radiolabeled endosulfan dosing suspension (94.6% ai) at nominal doses of 0.1, 1, and 10 mg/kg and exposed for 0.5, 1, 2, 4, 10 and 24 hours. After exposure, the application sites were washed with 5 ml of mild soap solution and three 5 ml portions of water for further analysis. The percent doses absorbed over a 24-hour period were 2.2-21.6, 0.32-21.52, and 0.08-8.38 for the 0.1, 1, and 10 mg/kg dose groups, respectively. The percentages of endosulfan absorbed at 1, 10 and 24 hours intervals, were 1.8, 7.6 and 21.6% for rats dosed at 0.1 mg/kg, 0.57, 5.77 and 21.52%, for rats dosed at 1.0 mg/kg, and 0.29, 3.86, and 8.38% for rats dosed at 10 mg/kg. The percent doses remaining in/on the skin after soap and water washes over a 24-hour period were 62.1-56.5, 78.1-57.7, and 80.2-66.7 for the 0.1, 1, and 10 mg/kg dose groups, respectively. These data showed that significant portions of the dose remained on the skin following soap and water washes. At the 24-hour interval, the data showed endosulfan bioaccumulating in the body of the rats.

In another dermal absorption study (MRID#41048504), three groups of 16 female Crl:CD(SD)BR rats/group were dosed topically with radiolabeled endosulfan (94.6% ai) at nominal doses of 0.1, 1, and 10 mg/kg (1.9, 21.9, and 231.4 mg/cm2) to determine the fate of the residue that was left in/on the skin following 10 hours of exposure. Ten hours after dosing, the application sites were washed with 1% liquid Ivory soap and rinsed with water. The radioactive labeled endosulfan presence was analyzed in four live rats/group at 24, 48, 72, and 168 hours after dosing. The percent dose absorbed at 24 hours was 22.1, 16.1, and 3.8% and at 168 hours was 44.8, 46.4, and 20.3% for the 0.1, 1, and 10 mg/kg dose groups, respectively. The amount of the dose remaining on/in the skin at 168 hours was 41.4, 56.2, and 72.8% for the 0.1, 1, and 10 mg/kg dose groups, respectively. The data showed that endosulfan bioaccumulates in the body of the rats.

The HIARC selected the dermal absorption factors of 45 % (rounded from 44.8%) at 168 hours post exposure. The Committee selected the dermal absorption rate based on the following weight-of-evidence considerations: 1) at 24 hours, the percent absorption was comparable between males (21.6%) and females (22.1%); 2) in female rats, even after washing at 10 hours, the percent absorption increased with time, the final measurement was 44.8% at 168 hours; 3) the concern that the test material continued to be absorbed even after washing at 10 hours; 4) substantial dermal absorption was demonstrated in the 21-day dermal toxicity study with a NOAEL of 3 mg/kg/day and systemic toxicity (increased mortality, and increased liver abnormalities) evident at 9 mg/kg/day (LOAEL). In addition, this dermal absorption factor is supported by comparing the results of the oral and dermal studies in the same species. The ratio of the oral LOAEL of 6 mg/kg/day in the developmental toxicity study in rabbits and the dermal LOAEL of 9 mg/kg/day in the 21-day dermal toxicity study in rabbits with the same endpoint

(increased mortality) indicate a dermal absorption rate of 67% [(6 ÷9] x 100 = 67%) as compared to the amount absorbed orally.

Dermal Absorption Factor = 45%

3.6.4 Short-term (1-30 days) Dermal Occupational Exposures

In a 21-day dermal toxicity study (ACC # 257684/257685) in rats, endosulfan (97.2% ai w/w) was applied to the skin of five groups of six male and female Wistar rats at doses of 0, 1, 3, 9, and 27 mg/kg/day and onto six males only at 81 mg/kg/day, for 21 applications (5 days a week) over 30 days. Five of the six (83%) high-dose (27 mg/kg/day) females died on days 2 and 6 of the study. Three of the six (50%) high-dose (81 mg/kg/day) males died on days 2 and 3 of study (females were not tested at this dose). Two of the three 81 mg/kg/day males that died had shown tonoclonic convulsions, increased salivation and respiration. Although no deaths occurred in males dosed at 27 mg/kg/day, 2 of the 6 (33%) males dosed at 9 mg/kg/day died on days 5 and 8. Prior to death, one male rat showed salivation, blood-encrusted nose, dyspnea and staggered gait and these symptoms are related to treatment. Also, these deaths are significantly increased over the controls which showed no mortality. Increased incidence of mortality in males dosed at 9 and 81 mg/kg/day and females dosed at 27 mg/kg/day appear to be a compound-related effect. No changes of clinical chemistry and hematology parameters can be attributed to treatment. Changes that occurred were small and they are not judged to be dose-related. Changes in liver cells in 2 of six males were found at 9 mg/kg/day dose levels and above. Liver abnormalities included enlargement of parenchymal cells in peripheral sections, together with a loss of cytoplasmic basophilia, isolated cell necrosis, and frequent mitosis. Females dosed at 9 mg/kg/day showed significantly increased absolute and relative spleen and absolute adrenal weights, as compared to controls. Significant dermal irritation was not produced by the test compound. Dermal irritation for all groups was very slight at all evaluation intervals. It appears that dermal irritation was more persistent in females at 3 and 9 mg/kg/day dose groups, as evidenced by greater dermal irritation scores (2-3 times) than that of controls. There was no difference between the average scores of the treated males as compared to the controls at any dose level. Although dermal irritation scores were zero at the end of the study, and although the pathology report described that dermal effects were similar in treated and control animals, there appears to be an increase in severity or prolongation of irritation found in females dosed at 3 and 9 mg/kg/day. The NOAEL for this study was 3 mg/kg/day and the LOAEL was 9 mg/kg/day for systemic toxicity based on increased mortality with clinical signs in males, and increased liver abnormalities (enlargement of parenchymal cells, loss of cytoplasmic basophilia and isolated cell necrosis and frequent mitosis) in both sexes. Increased absolute spleen weight and deaths also occurred in the 27 mg/kg/day female rats.

The dose and endpoint selected for risk assessment was dermal NOAEL= 3 mg/kg/day based on mortality with clinical signs in males, and increased liver abnormalities (enlargement of parenchymal cells, loss of cytoplasmic basophilia and isolated cell necrosis and frequent mitosis) in both sexes at 9 mg/kg/day (LOAEL). This 21-day dermal study is appropriate for dermal

exposure scenarios up to 30 days. The toxicity endpoint is supported by another 21-day dermal toxicity study (MRID 41048505) in which clinical signs (tremors, straub-tail, spasms) and mortality occurred in female rats treated dermally with 12 mg/kg of a formulation (33.3% ai) of endosulfan. A Margin of Exposure (MOE) of 100 (10x for inter-species extrapolation and 10x for intra-species variability) is adequate for occupational exposure.

short-term dermal occupational MOE = 100

3.6.5 Intermediate (one to several months)/Long (several months to 1 year)-term Dermal Occupational Exposures

The 21-day dermal toxicity study in rats (ACC.# 257684/257685) was also selected for intermediate/long-term dermal exposure. See Short-Term Dermal Occupational Exposures above. The dose and endpoint selected for risk assessment is dermal NOAEL= 3 mg/kg/day based on mortality with clinical signs in males, and increased liver abnormalities (enlargement of parenchymal cells, loss of cytoplasmic basophilia and isolated cell necrosis and frequent mitosis) in both sexes at 9 mg/kg/day (LOAEL).

The 21-day dermal study can also be used for intermediate-/long-term dermal risk assessments because of the appropriateness for the route of exposure and the toxicity is defined and characterized. There is sufficient evidence to believe that endosulfan bioaccumulates with repeated exposure and its toxicity to target organs increases with duration. Endosulfan is structurally similar to other polychlorinated cyclodienes (aldrin, dieldrin, chlordane) which are well known for their toxicities and persistence, slow rate of metabolism, and bioaccumulation in animal tissue. The Committee believes that the severity of the toxicity noted in the 21-day dermal study would increase with duration. This is demonstrated in long term oral studies where the severity and incidence of toxicity (body weight decrease and kidney disease) progresses in the 2-year chronic toxicity study in rats.

An MOE of 100 (10x for inter-species extrapolation and 10x for intra-species variability) is generally adequate for occupational exposure. However, in the absence of dermal toxicity studies beyond 30 days exposure, the HIARC requires an additional (FIFRA) factor of 3x to address the uncertainty in extrapolating data from less than 30 days up to several months and/or years, for a total MOE of 300. Since the ETF is not supporting any of the uses that may have resulted in long-term exposures, no long-term exposures are expected.

intermediate/long-term dermal occupational MOE = 300

3.6.6 Short-term (1-30 days) Inhalation Occupational Exposures

In a range-finding inhalation study (MRID 41667501) two groups of 5 Wistar rats/sex were exposed, nose-only, to aerosol concentrations of endosulfan (97.2% ai) at 0.0024 and 0.0065 mg a.i./L for 6 hours/day, five days/week for a total of 7 exposures. Two females exposed

to 0.0065 mg/L died by day 8 of the study. Female survivors had clinical signs including tremors, trembling, tonic-clonic convulsions, and reduced corneal reflexes. Males exposed to the highest concentration were ataxic and had irregular breathing. Body weight loss was noted in males and females at both concentrations early in the study (days 3-4). Based on the results of this range finding study, the highest concentration for the 21-day subchronic study was set at 0.0020 mg a.i./L. In the 21-day inhalation toxicity study (MRID# 00147183), ten male and ten female Wistar rats were exposed, nose-only, to technical endosulfan (97.2% ai) at concentrations of 0 (air), 0.0005, 0.0010, and 0.0020 mg/L (0.097, 0.194, and 0.387 mg/kg/d)[1] for 6 hours/day, 5 days/week for a total of 21 exposures over 29 days. An additional group of 5 animals/sex/dose was held for a 4-week recovery period after receiving the test aerosol. No mortality or clinical signs of toxicity occurred during the study. Group mean body weights were similar to controls with the exception of males in the highest dosed group that had lower body weight (3-5%) from day 20 through 29. In the highest dosed males from the recovery group, the decrements in body weights were more pronounced (12-16%) from recovery days 34-60. Although neither sex had any statistically significantly body weight changes during the exposure period and the number of recovery animals for each sex was only 5, the apparent effect suggested a possible delay in its manifestation.

Erythrocyte counts in the low and mid dose males at the end of the exposure period (Day 29) were significantly elevated. No effects on erythrocyte counts were observed at the high dose. Hence, the changes did not demonstrate a pattern of toxicity. In addition, the test report stated that the values were apparently within the norm for the species and strain studied. Some slight effects on clinical chemistry and in hematology counts were noted but these did not demonstrate significant toxicity of the test compound. There were statistically significant decreases in leucocyte counts (20.1%) in the high-dose males, which seemed to be marginally dose related but did not indicate significant toxicity. High-dose females had increased creatinine (21%) values suggestive of kidney toxicity and were judged to be treatment related but there were no other signs supporting kidney toxicity in the histopathology or organ weight changes. The study NOAEL was 0.0010 mg a.i./L (0.20 mg/kg/day), and the LOAEL was 0.0020 mg a.i./L (0.40 mg/kg/day) based on decreased body-weight gain and decreased leukocyte counts in the males and increased creatinine values in the females.

The dose and endpoint selected for risk assessment was NOAEL = 0.0010 mg a.i./L (0.2 mg/kg/d) based on decreased body-weight gain and decreased leukocyte counts in males and increased creatinine values in females at the LOAEL of 0.0020 mg a.i./L (0.4 mg/kg/d). The inhalation study in rats is route appropriate for the short-term inhalation exposure up to 30 days and the toxicity effects (decreased body weight gain and nephrotoxicity) are noted in other longer term studies by the oral route. Because endosulfan has appreciable lipophilicity it is likely to bioaccumulate in fatty tissue and it is expected that increased toxicity to target organs will occur

---

[1] Conversion of mg/L to oral dose (mg/kg/day) = mg/L x absorption (1.0) x [Respiratory Volume (Wistar rats) for 6 hours/day] x Duration of Exposure (5 days/wk)/ body weight x 7 days/week

$$= \frac{0.001 \text{ mg/L} \times 1.0 \times [8.46(\text{RV}) \times 6 \text{ hrs}) \times 5 \text{ d/wk}}{0.187 \text{ kg} \times 7 \text{ d/wk}} = 0.194 \text{ mg/kg/day}$$

over longer periods of exposure. A Margin of Exposure (MOE) of 100 (10x for inter-species extrapolation and 10x for intra-species variability) is adequate for occupational exposure.

short-term inhalation occupational MOE = 100

3.6.7 Intermediate (one to several months)/Long (several months to 1 year)-Term Inhalation Occupational Exposures

The 21-day inhalation study (MRID# 00147183)in the rat was also selected for the intermediate/long-term endpoint. See Short-Term Inhalation Occupational Exposures above. The dose and endpoint for risk assessment was NOAEL = 0.0010 mg a.i./L (0.2 mg/kg/d) based on decreased body-weight gain in both sexes and decreased leukocyte counts in males and increased creatinine values in females at the LOAEL of 0.0020 mg a.i./L (0.4 mg/kg/d).

The 21-day study is also appropriate for intermediate-/long-term exposure scenarios because of the route of exposure. The toxic effects (decreased body weight gain and increased creatinine in females) are appropriate early markers for the effects observed in rats following long-term oral exposure (decreased body weight and kidney disease). There is sufficient evidence to believe that endosulfan bioaccumulates with repeated exposure. Endosulfan has structural relationship to other polychlorinated cyclodienes (aldrin, dieldrin, chlordane) which are well known for their toxicities, persistence, slow rate of metabolism and bioaccumulation in animal tissue. Evidence for cumulative toxicity is further demonstrated in this inhalation study in which decrements in body weights were more pronounced in males given 0.0020 mg/L (LOAEL) during recovery following cessation of endosulfan treatment. The apparent effect suggested an accumulation in the manifestation of the toxicity following repeated exposure to endosulfan. Again, since there are no subchronic (>30 days) or chronic inhalation studies and there is sufficient evidence to indicate that long term exposure increases toxicity in target organs, the HIARC recommended a (FIFRA) factor of 3x be applied to account for the uncertainty in extrapolating from a 21-day study to exposures of several months and/or years. Therefore, a total MOE of 300 (10x for inter-species extrapolation, 10x for intra-species variability, and 3x for uncertainty) is adequate for long-term inhalation occupational exposure. No long-term exposures are expected at this time.

intermediate/long-term inhalation occupational MOE = 300

3.6.8 Carcinogenic Potential

There was no evidence of oncogenicity in either the combined chronic toxicity/ oncogenicity study in rats (MRID# 41099502) or the oncogenicity study in mice (MRID# 40792401). The doses were considered adequate in both studies. Endosulfan technical was also inactive in the primary rat hepatocyte unscheduled DNA synthesis (UDS) assay (MRID# 00148265), and was non-mutagenic in the mouse lymphoma forward mutation assay (MRID# 00148266). Endosulfan is classified as “not likely” a human carcinogen.

Table 3. Summary Endpoint Selection for Endosulfan

Exposure Scenario	Dose Used in Risk Assessment, UF and FQPA SF	Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary: 1) females 13-50 years of age 2) infants and children	oral NOAEL= 1.5 mg/kg/day UF = 100 **Acute RfD** = 0.015mg/kg/day FQPA SF = 3x	**aPAD** = acute RfD / FQPA SF = 0.005 mg/kg/day	Acute neurotoxicity study (rats): oral NOAEL = 1.5 mg/kg/day; oral LOAEL = 3 mg/kg/day; based on increased incidence of convulsions seen in female rats within 8 hours after dosing (3 mg/kg). UF of 100 applied for intra- (10x) and interspecies (10x) differences. FQPA SF of 3X applied.
Acute Dietary: general population	oral NOAEL= 1.5 mg/kg/day UF = 100 **Acute RfD** = 0.015 mg/kg/day FQPA SF = 1x	**aPAD** = acute RfD / FQPA SF = 0.015 mg/kg/day	Acute neurotoxicity study (rats): oral NOAEL = 1.5 mg/kg/day; LOAEL = 3 mg/k/day; based on increased incidence of convulsions seen in female rats within 8 hours after dosing (3 mg/kg). UF of 100 applied for intra- (10x) and interspecies (10x) differences. FQPA SF of 1X applied.
Chronic Dietary: 1) females 13-50 years of age 2) infants and children	oral NOAEL = 0.6 mg/kg/day UF = 100 **Chronic RfD** = 0.006 mg/kg/day FQPA SF = 3x	**cPAD** = chronic RfD / FQPA SF = 0.002 mg/kg/day	Chronic (2-year) toxicity/carcinogenicity study (rats): Oral NOAEL = 0.6 mg/kg/day; LOAEL = 2.9 mg/kg/day based on reduced body weight gain, increased incidences of marked progressive glomerulonephrosis and blood vessel aneurysms in male rats. UF of 100 applied for intra- (10x) and interspecies (10x) differences. FQPA SF of 3X applied.
Chronic Dietary: general population	NOAEL = 0.6 mg/kg/day UF = 100 **Chronic RfD** = 0.006 mg/kg/day FQPA SF = 1x	**cPAD** = chronic RfD / FQPA SF = 0.006 mg/kg/day	Chronic (2-year) toxicity/carcinogenicity study (rats): Oral NOAEL = 0.6 mg/kg/day; LOAEL = 2.9 mg/kg/day based on reduced body weight gain, increased incidences of marked progressive glomerulonephrosis and blood vessel aneurysms in male rats. UF of 100 applied for intra- (10x) and interspecies (10x) differences. FQPA SF of 1X applied.

Exposure Scenario	Dose Used in Risk Assessment, UF and FQPA SF	Endpoint for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal (1-30 days) Occupational: handler and postapplication exposure	dermal NOAEL = 3.0mg/kg/day	**Target MOE** = 100	21-day rat study, endosulfan applied dermally: dermal NOAEL = 3.0 mg/kg/day; LOAEL = 9 mg/kg/day, based on increased mortality and increased liver abnormalities in both sexes. UF of 100 applied for intra- (10x) and interspecies (10x) differences.
Intermediate-Term Dermal (one to several months) Occupational: handler and postapplication exposure)	dermal NOAEL = 3.0mg/kg/day	**Target MOE** = 300 for exposures > 30 days	21-day rat study, endosulfan applied dermally: dermal NOAEL = 3.0mg/kg/day; LOAEL = 9 mg/kg/day, based on increased mortality and increased liver abnormalities in both sexes. UF of 300 applied for intra- (10x) and interspecies (10x) differences plus 3x for lack of longer-term study.
Long-Term Dermal (several months to 1 year) Occupational: postapplication exposure only	dermal NOAEL = 3.0mg/kg/day	**Target MOE** = 300	21-day rat study, endosulfan applied dermally: dermal NOAEL = 3.0mg/kg/day; LOAEL = 9 mg/kg/day, based on increased mortality and increased liver abnormalities in both sexes. UF of 300 applied for intra- (10x) and interspecies (10x) differences plus 3x for lack of longer-term study .
Short-Term Inhalation (1-30 days) Occupational: handler and postapplication exposure	inhalation NOAEL = 0.2 mg/kg/day (= 0.0010 mg/L)	**Target MOE** = 100	21-day rat inhalation study:NOAEL = 0.0010 mg/L (= 0.2 mg/kg/day). LOAEL = 0.0020 mg/L (= 0.387 mg/kg/day), based on decreased body weight gain and decreased leukocyte counts in males , and increased creatinine values in females. UF of 100 applied for intra- (10x) and interspecies (10x) differences.

Exposure Scenario	Dose Used in Risk Assessment, UF and FQPA SF	Endpoint for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Inhalation (one to several months) Occupational: handler and postapplication exposure	inhalation NOAEL = 0.2 mg/kg/day (= 0.0010 mg/L)	**Target MOE** = 300 for exposures > 30 days	21-day rat inhalation study: NOAEL = 0.0010 mg/L (= 0.2 mg/kg/day). LOAEL = 0.0020 mg/L (= 0.387 mg/kg/day), based on decreased body weight gain and decreased leukocyte counts in males , and increased creatinine values in females. UF of 300 applied for intra- (10x) and interspecies (10x) differences plus 3x for lack of a longer-term study.
Long-Term Inhalation (several months to 1 year) Occupational: postapplication exposure only	inhalation NOAEL = 0.2 mg/kg/day (= 0.0010 mg/L)	**Target MOE** = 300	21-day rat inhalation study: NOAEL = 0.0010 mg/L (= 0.2 mg/kg/day). LOAEL = 0.0020 mg/L (= 0.387 mg/kg/day), based on decreased body weight gain and decreased leukocyte counts in males , and increased creatinine values in females. UF of 100 applied for intra- (10x) and interspecies (10x) differences plus 3x for lack of a longer-term study.

3.7 Endocrine Disruption

The FQPA (1996) requires that the Agency develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect....." The Agency has been working with interested stakeholders that include other government agencies, public interest groups, industry, and research scientists to develop a screening and testing program, as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disruptor Screening Program was published in the Federal Register of December 28, 1998 (63 FR 71541). This Program uses a tiered approach and anticipates issuing a priority list of chemicals and mixtures for Tier 1 screening in the year 2001.

The potential for endosulfan to cause changes in endocrine function was evaluated from the results of the OPPTS guideline studies described above and studies available in the published literature. A detailed review of the study results used in the evaluation is available (*Toxicology Chapter for Endosulfan RED*. Nicole Paquette, and David Liem, November 22, 1999). In the process of this evaluation, endosulfan was identified as a potential endocrine disruptor.

One of the ETF members, AgrEvo, submitted a literature review (MRID# 44939102) in

response to the Agency's characterization of the endosulfan database as providing "suggestive evidence that endosulfan may be an endocrine disruptor." After reviewing several published articles, the registrant concluded that "endosulfan does not meet the criteria of an endocrine disruptor." The registrant stated that *in vitro* studies show that endosulfan has a low binding potency to the human estrogen receptors and that "no effects were found on endocrine, reproductive or sexually regulated systems *in vivo* at doses causing clear toxicity."

The Agency identifies an environmental endocrine disruptor as an exogenous agent that interferes with the synthesis, secretion, transport, binding action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (Crisp et al. 1998). Based on these criteria, the Agency disagrees with the conclusion by the registrant that endosulfan does not meet the definition of an endocrine disruptor (ENDOSULFAN: Evaluation of Registrant Submission *Endosulfan: Evaluation of Possible Endocrine Effects in Mammalian Species*. Elizabeth Mendez, December 11, 2000). Binding to the estrogen receptor is only one potential mode of action for endocrine disruptors, namely direct interaction with a receptor in the target cells. Substances that act as endocrine disruptors may perturb the endocrine system in a variety of ways, including but not limited to, interfering with the synthesis, secretion, or transport of hormones in the organism. Consequently, the absence of high binding affinity to the estrogen receptor should not be interpreted as lack of endocrine disruption potential. The Agency notes that other organochlorines (i.e. DDT, DDE, dieldrin, and methoxychlor) have been demonstrated to interact with the endocrine system in spite of differing binding affinities to the estrogen receptor. Finally, the registrant stated that no effects were reported after administration of endosulfan on the endocrine, reproductive or sexually regulated systems at doses causing clear toxicity. However, it is noteworthy that testicular atrophy was reported during a chronic oral toxicity study in rats (MRID# 00004256) submitted to the Agency. Additionally, increased pituitary and uterine weights were also observed during a multi-generation reproduction study (MRID# 00148264). Furthermore, an increase in the incidence of parathyroid hyperplasia was also reported during the chronic oral toxicity study in rats. The Agency emphasizes the fact that the endocrine system integrates a variety of CNS-pituitary-target organ pathways that not only affect reproductive or sexually regulated parameters but also regulates a wide array of bodily functions and homeostasis (Cooper and Kavlock 1997). Though this is not the case for endosulfan, it is important to note that a lack of overt toxicity to the reproductive system should not be interpreted as conclusive evidence of a lack of endocrine disruption. Given the effects noted in the chronic oral toxicity study in rats and the multi-generation reproduction study submitted to the Agency, the potential of endosulfan to act as an endocrine disruptor cannot be discounted. The Agency has requested that a Developmental Neurotoxicity Study be conducted; the Agency believes that this study will provide additional data that may help elucidate this matter.

The Agency has not yet completed its development of the criteria that it will use for characterizing and prioritizing endocrine disrupting substances. As the Agency proceeds with implementation of its Endocrine Disruptor Screening Program, additional testing of endosulfan may be requested.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Uses

At this time, products containing endosulfan are registered for occupational and residential uses; however, as mentioned earlier, the ETF is not supporting residential uses and they have not been included in this assessment. Occupational uses include applications to agricultural food and non-food crops, ornamental and/or shade trees, fruit and nut crops, ornamental herbaceous trees, and shrubs.

Endosulfan is formulated for occupational use as a technical grade manufacturing product (95% active ingredient [ai]), emulsifiable concentrate (9 - 34% ai), and a wettable powder (1 - 50% ai). The wettable powder is frequently packaged in water soluble bags. Depending on the crop to be treated and the formulation to be used, formulations containing endosulfan may be applied by groundboom sprayer, fixed-wing aircraft, chemigation (potatoes only), airblast sprayer, rights of way sprayer, low pressure handwand, high pressure handwand, backpack sprayer, and dip treatment. The application rate and number of allowable applications varies, depending upon use (*Second Revision of "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Endosulfan*, Renee Sandvig, January 2, 2001). On the majority of product labels, the number of maximum allowable applications ranges between 1 and 3 per season or year, and does not exceed 5.

Endosulfan has been registered for occupational-use on terrestrial food and feed crops, indoor food crops, and terrestrial non-food crops. The occupational use sites included in this assessment (not subject to the 6F Use Deletion Notices) have been grouped as follows (Table 8):

- *Vegetables and Field Crops*: alfalfa (seed only), barley, beans (dry and succulent), blueberries, broccoli, brussels sprouts, cabbage, carrots, cauliflower, celery, clover (seed only), collards, cotton, corn (fresh only), cucumbers, eggplants, grapes, kale, kohlrabi (seed only), lettuce, melons, mustard greens, oats, peas, peppers, pineapples, potatoes, pumpkins, radish (seed only), rutabaga (seed only), rye, spinach, squash, sweet potatoes, strawberries, tobacco, tomato, turnip, and wheat.

- *Fruit and Nut Trees (orchard crops)*, including apples, apricots, almonds, cherries, filberts, macadamia nuts, nectarines, pecans, peach, pear, plums, prunes, and walnuts.

- *Ornamental Trees and Shrubs*, including shade trees, citrus (non-bearing), shrubs, nursery stock, Christmas tree plantations, and woody plants.

- *Root dip*, including cherry, peaches, and plum roots and crowns, and whole strawberry plants.

- *Agriculture in greenhouses* (tomatoes and ornamental trees and shrubs).

The crop groupings with their corresponding maximum label application rates are as follows (both formulations unless noted, EC = emulsifiable concentrate, WP = wettable powder formulations):

- *Agricultural crops, including vegetables and field crops*: alfalfa (seed only, 1 lb ai/A EC), barley, rye, oats and wheat (0.75 lb ai/A), beans and tomatoes (1 lb ai/A), clover (0.5 lbs ai/A EC), blueberries (1.5 lb ai/A), broccoli, cabbage, collard, lettuce, melons, and mustard greens (1lb ai/A or 2 lb ai/A for seed), brussels sprouts, carrots, cauliflower, celery, cucumbers, eggplants, peas, peppers, potatoes, pumpkins, spinach, and squash (1 lb ai/A), cotton and corn (fresh only) (1.5 lb ai/A), grapes (1.5 lb ai/A or 0.005 lb ai/gallon), kale (0.75 lb ai/A or 2 lb ai/A for seed), kohlrabi, radish, turnip and rutabaga (2 lb ai/A seed only), pineapples and sweet potato (2 lb ai/A), and tobacco (1.5 lb ai/A WP, 3 lbs ai/A EC).

- *Fruit and nut trees (orchard crops)*, including apples (2.5 lb ai/A or 0.0075 lb ai/gal), apricots, peach, and nectarines (3 lb ai/A or 0.0025 lb ai/gal), almonds (2.5 lb ai/A or 0/025 lb ai/gallon), cherries, pears, plums, and prunes (2.5 lb ai/A or 0.04 lb ai/gallon), filberts (hazelnuts 2lb ai/A or 0.005 lb ai/gallon), macadamia nuts and pecans (7.5lb ai/A or 0.075 lb ai/gallon), and walnuts (2 lb ai/A or 0.02 lb ai/gallon WP, 2.5 lb ai/A or 0.04 lb ai/gallon EC).

- *Ornamental Trees and Shrubs*, including shade trees, citrus (non-bearing and nursery stock), shrubs, nursery stock, Christmas tree plantations, and woody plants (1 lb ai/A or 0.01 lb ai/gallon).

- *Root dip*, including cherry, peaches, and plum roots and crowns (0.05 lb ai/gallon) and whole strawberry plants (0.01 lb ai/gallon EC).

- *Bark Treatment*, includes apricot, cherry, grapes, nectarines, peach, plums and prunes (see above for application rates, applied with high pressure handwands and rights-of-way sprayers).

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Endosulfan is currently registered for food/feed uses on a variety of field, fruit, and vegetable crops. In a meeting held on April 21, 1997 the Metabolism Assessment Review Committee (MARC) concluded that the residues of toxicological concern are endosulfan and the sulfate metabolite; therefore, tolerances for crop and livestock commodities should be expressed

as residues of the parent and the sulfate metabolite. The MARC also recommended that the tolerance expression be revised to specify the á- and â- isomers of endosulfan. The published tolerances for endosulfan (alpha and beta isomers) [6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide] and its metabolite endosulfan sulfate [6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3,3-oxide] are listed in 40 CFR §180.182.

Tolerances have been established for residues of endosulfan in/on various plant and animal commodities under 40 CFR §180.182 and in processed food commodities under 40 CFR §185.2600. These tolerances range from 0.1 - 24 ppm and are currently expressed in terms of endosulfan and its metabolite, endosulfan sulfate. Adequate methods are available for data collection and tolerance enforcement. Codex maximum residue limits (MRL)s are expressed as the sum of á- and â-endosulfan and endosulfan sulfate [*Revised Residue Chemistry Chapter for the Endosulfan Reregistration Eligibility Decision (RED) Document*. John Punzi, January 3, 2001].

Dietary risk estimates are based, in part, on estimates of the percent usage of endosulfan on each registered crop. BEAD has estimated endosulfan use (*Quantitative Usage Analysis for Endosulfan. Steven Nako, October 13, 1999; Updated QUA.* David Donaldson, September 10, 2000) based on available pesticide survey usage data for the years 1987 through 1998. BEAD estimates are provided to HED as a weighted average and as an estimated maximum. This risk assessment assumed 1% CT for any BEAD estimate less than 1%. The estimated maximum %CT for each commodity was used for the acute risk assessment and the estimated weighted average %CT for each commodity for the chronic dietary risk assessments. Where no further information was available, 100 %CT was assumed.

Endosulfan residue estimates, or anticipated residues (AR) in this assessment are based primarily on three data sources: 1) field trial data, submitted by the registrant to support tolerances; 2) USDA PDP food sampling data; and 3) FDA Surveillance Monitoring data. Where data were not available, tolerance levels were used incorporating the %CT estimates from BEAD. The order of preference for the purpose of risk assessment is: PDP data > FDA data > field trial data > tolerance. PDP data are preferred over FDA data because the statistical design of the PDP program is specific for dietary risk assessment (i.e. sampling is done at grocery store distribution points instead of directly from the field), and because the foods are prepared before analysis as they would typically be before consumption (i.e. peeling, washing). Many endosulfan treated commodities not sampled by the PDP program are assessed based on translation of data from PDP sampled commodities in the same crop group, FDA surveillance data, or field trial data where available. Tolerance values were used for mustard seed, sugarcane, and watercress. Field trial residue data are generally considered by HED as an upper-end or a worse case scenario of possible residues and are more suited to the requirements of tolerance setting, because it requires highest rates of application and shortest PHI, than to the requirements of dietary risk assessment (when the most realistic estimate is desired).

Potential transfer of pesticide residues from treated feed items to livestock commodities are estimated by calculating a livestock dietary burden, and are based on livestock feeding studies conducted at the appropriate dose levels. For endosulfan, HED estimated a realistic dietary burden to cattle using the following formula: Dietary burden (ppm) = % of Diet/ % Dry Matter X Anticipated Residue (ppm). The ARs calculated for beef cattle were also used in this dietary assessment for goat, horse, rabbit, sheep, and veal. HED used PDP data (1996-97) for milk which showed all residues to be less than the level of detection (LOD 0.001 ppm). The chronic AR for milk incorporated ½LOD for parent (á- and â- isomers) and metabolite (endosulfan sulfate); however, for the acute dietary assessment, a residue data file was used for milk which also incorporated ½LOD for each parent (á- and â- isomers) and metabolite. Potential transfer of pesticide residues from treated feed items to swine commodities were estimated by calculating a swine dietary burden based on submitted swine feeding studies. No endosulfan tolerances are established in eggs and poultry tissues. Submitted poultry feeding data suggest that there is no reasonable expectation of finite residues; therefore, eggs and poultry were not included in this dietary assessment (CFR §180.683).

4.2.2 Acute Dietary

To estimate acute dietary exposure, one-day consumption data were summed and a food consumption distribution was calculated for the general population and each population subgroup of interest. The consumption distribution was used with a residue distribution in a Tier III probabilistic-type (Monte Carlo) exposure assessment. Exposure estimates were expressed in mg/kg/day.

To assess human health risks resulting from consumption of foods that contain residues of endosulfan, estimates of acute dietary food exposure of the general population and specific population subgroups were compared to the aPAD. The risk estimate for a given population is made from a comparison of the anticipated dietary food exposure of the population to the aPAD established for that population. Dietary exposure is expressed as a percentage of the aPAD (anticipated exposure ÷ PAD x 100 = % PAD). Dietary exposure estimates that exceed the aPAD values (i.e., that are greater than 100% of the PAD) are of concern to the Agency.

The results of the acute dietary food exposure and risk estimates are shown in Table 4a&b. As can be seen from the tables, children 1-6 years of age are the most highly exposed to endosulfan residues from consumption of foods. Estimated acute dietary exposure to children 1-6 years does not exceed the aPAD at the 95th, 99th, and 99.9th exposure percentiles. A complete listing of the acute dietary results can be found in *Revised Anticipated Residues, Acute and Chronic Dietary Exposure Analyses for Endosulfan.* Sherrie Kinard, December 15, 2000. Several crops have been identified as making significant contributions to the dietary risk. Residues measured on these crops and the surveyed consumption of these crops, factored together, result in these crops taking up a significant percentage of the aPAD and thereby, making significant contributions to the risk. A number of crops had significant residues from monitoring data and are high consumption items (e.g. succulent green beans). The significant acute contributors have

been identified as cucumbers (uncooked and canned: cured), garden green peas (boiled), lettuce head varieties (uncooked), and succulent green beans (boiled). For all the significant contributors, PDP and/or FDA monitoring data have shown measurable residues of endosulfan, some greater than tolerance.

Table 4a. Summary of Tier III Endosulfan Acute Dietary Food Exposure Estimates[a] and Risk Assessments without Using Weighted FDA Data

Population	aPAD	(95th percentile)		(99th percentile)		(99.9th percentile)	
		Exposure mg/kg/d	% aPAD	Exposure mg/kg/d	% aPAD	Exposure mg/kg/d	% aPAD
U.S. Population	0.015 mg/kg	0.000120	<1	0.000364	2	0.001882	13
All Infants <1 year	0.005 mg/kg	0.000183	4	0.000395	8	0.001809	36
Children 1-6 years	0.005 mg/kg	0.000222	**4**	0.000632	**13**	0.003511	**70**
Children 7-12 years	0.005 mg/kg	0.000151	3	0.000452	9	0.002321	46
Females 13-50 years	0.005 mg/kg	0.000089	2	0.000295	6	0.001559	31
Females 20+ years	0.015 mg/kg	0.000088	<1	0.000325	2	0.001717	11
Males 13-19 years	0.015 mg/kg	0.000103	<1	0.000295	2	0.001477	10
Males 20+ years	0.015 mg/kg	0.000095	<1	0.000301	2	0.001519	10
Seniors 55+ years	0.015 mg/kg	0.000090	<1	0.000367	2	0.001847	12

[a] Exposure estimates include exposure to all endosulfan residues of toxicological concern (i.e., á-endosulfan, â-endosulfan, and endosulfan sulfate).

Table 4b. Summary of Tier III Endosulfan Acute Dietary Food Exposure Estimates[a] and Risk Assessments Using Weighted FDA Data

Population	aPAD	(95th percentile)		(99th percentile)		(99.9th percentile)	
		Exposure mg/kg/d	% aPAD	Exposure mg/kg/d	% aPAD	Exposure mg/kg/d	% aPAD
U.S. Population	0.015 mg/kg	0.000110	<1	0.000304	2	0.001380	9

Population	aPAD	(95th percentile)		(99th percentile)		(99.9th percentile)	
		Exposure mg/kg/d	% aPAD	Exposure mg/kg/d	% aPAD	Exposure mg/kg/d	% aPAD
All Infants <1 year	0.005 mg/kg	0.000182	4	0.000394	8	0.001533	31
Children 1-6 years	0.005 mg/kg	0.000206	**4**	0.000531	**11**	0.002552	**51**
Children 7-12 years	0.005 mg/kg	0.000139	3	0.000385	8	0.001734	35
Females 13-50 years	0.005 mg/kg	0.000081	2	0.000243	5	0.001156	23
Females 20+ years	0.015 mg/kg	0.000079	<1	0.000261	2	0.001245	8
Males 13-19 years	0.015 mg/kg	0.000095	<1	0.000246	2	0.001056	7
Males 20+ years	0.015 mg/kg	0.000086	<1	0.000247	2	0.001120	7
Seniors 55+ years	0.015 mg/kg	0.000080	<1	0.000281	2	0.001314	9

[a] Exposure estimates include exposure to all endosulfan residues of toxicological concern (i.e., á-endosulfan, â-endosulfan, and endosulfan sulfate).

4.2.3 Chronic Dietary

For chronic dietary risk assessments, residue estimates for foods (e.g. apples) or food-forms (e.g. apple juice) of interest are multiplied by the averaged consumption estimate of each food/food-form of each population subgroup. Exposure estimates are expressed in mg/kg bw/d and as a percent of the cPAD.

For the chronic dietary exposure assessment, residue data from USDA's PDP, FDA, or field trials were averaged. If a commodity had no reported detections by the PDP and FDA programs, and the expectation of no detection was confirmed by field trial data, the residue concentration was assumed to be the weighted average of one-half the LOD of each residue of toxicological concern (½ LOD á-endosulfan + ½ LOD â-endosulfan + ½ LOD endosulfan sulfate). For commodities with no detections from FDA data, half the LOQ was used for á-endosulfan, â-endosulfan, and endosulfan sulfate. The weighted average estimate of %CT was incorporated into all chronic residue estimates.

The results of the acute dietary food exposure and risk estimates are shown in Table 5a&b. Children 1-6 years of age have again been identified as the most highly exposed population

subgroup. Based on the chronic dietary exposure analysis as described above, chronic dietary exposure to all population subgroups does not exceed the cPAD. The chronic significant contributors have been identified as beef fat without bones, pasteurized milk based water, garden peas, and lettuce.

Table 5a. Summary of Tier III Endosulfan Chronic Dietary Food Exposure Estimates [a] and Risk Assessments without Using Weighted FDA Data

Population	cPAD mg/kg/day	Exposure (mg/kg/day)	% Chronic PAD
U.S. Population	0.006	0.000053	<1
All Infants (<1 year)	0.002	0.000061	3
Children 1-6 years	**0.002**	**0.000126**	**6**
Children 7-12 years	0.002	0.000080	4
Females 13-50 years	0.002	0.000039	2
Females 20+ years	0.006	0.000038	<1
Males 13-19 years	0.006	0.000054	<1
Males 20+ years	0.006	0.000041	<1
Seniors 55+ years	0.006	0.000052	<1

[a] Exposure estimates include exposure to all endosulfan residues of toxicological concern (i.e., á-endosulfan, â-endosulfan, and endosulfan sulfate).

Table 5b. Summary of Tier III Endosulfan Chronic Dietary Food Exposure Estimates [a] and Risk Assessments Using Weighted FDA Data

Population	cPAD mg/kg/day	Exposure (mg/kg/day)	% Chronic PAD
U.S. Population	0.006	0.000047	<1
All Infants (<1 year)	0.002	0.000060	3
Children 1-6 years	**0.002**	**0.000117**	**6**
Children 7-12 years	0.002	0.000073	4
Females 13-50 years	0.002	0.000034	2
Females 20+ years	0.006	0.000033	<1
Males 13-19 years	0.006	0.000050	<1
Males 20+ years	0.006	0.000036	<1
Seniors 55+ years	0.006	0.000046	<1

[a] Exposure estimates include exposure to all endosulfan residues of toxicological concern (i.e., á-endosulfan, â-endosulfan, and endosulfan sulfate).

4.2.4 Cancer Dietary

Endosulfan is classified as "not likely" a human carcinogen. Therefore, no dietary assessment for cancer risk was conducted.

4.3 Drinking Water Exposure/Risk Pathway

Based on the environmental fate properties of each isomer (á- and â-endosulfan), technical grade endosulfan represents a mixture of two chemically distinct pesticides which differ in persistence and volatility. Endosulfan is a persistent, semi-volatile compound that has been detected in nearly all environmental compartments, including surface- and ground-water and in areas where it is not used (e.g., the Arctic and national parks). The end-use product is a mixture of two endosulfan isomers, typically 70% á-endosulfan and 30% â-endosulfan. The â-isomer is generally more persistent and the á-isomer is more volatile. For both isomers, hydrolysis at pH values greater than 7 is an important degradation route; however, at pH values below 7, both isomers are rather persistent. At a pH of 7, á-endosulfan and â-endosulfan hydrolyze with half-lives of 11 and 19 days, respectively, and at a pH of 9, the isomers have half-lives of 4 to 6 hours. Some open literature studies indicate that the hydrolysis half-life may be somewhat longer (but of the same order of magnitude) at pH 7. Under acidic conditions, both isomers are stable to hydrolysis, and microbial degradation in soils becomes the predominant route of degradation. Half-lives in acidic to neutral soils range from one to two months for á-endosulfan and from three to nine months for â-endosulfan under aerobic conditions. Dissipation rates observed in field studies, which capture a combination of degradation, transport, and uptake, suggest that endosulfan will persist in the surface soil for weeks to months after application. Field dissipation rates were similar to those reported in laboratory soil metabolism studies.

The major transformation products found in the fate studies are endosulfan diol (hydrolysis) and endosulfan sulfate (soil metabolism). Both the diol and sulfate degradates have backbone structures similar to the parent compound and are also of toxicological concern. Available data suggest that endosulfan sulfate will be more persistent than the parent under all environmental conditions. The estimated half-lives for the combined toxic residues (endosulfan plus endosulfan sulfate) ranged from roughly 9 months to 6 years. See *EFED Risk Assessment for the Reregistration Eligibility Decision on Endosulfan (Thiodan)*, Nelson Thurman, et al., October 30, 2000.

Laboratory studies indicate that á- and â-endosulfan have a high affinity for sorption onto soil and are not expected to be highly mobile in the soil environment. However, because of endosulfan's resistance to degradation, it can persist long enough to be transported to both ground- and surface- waters, as monitoring studies have shown. Endosulfan can contaminate surface waters through spray drift and transport in runoff. In addition, endosulfan may move to

targets beyond its use area through atmospheric transport (via volatilization, transport on dust particles, or a combination). Within the water bodies, endosulfan tends to be sorbed onto sediment and plants. The sorbed endosulfan may be slowly released back into the water.

As mentioned above, the environmental fate profile for endosulfan indicates that both the á- and â-isomers of endosulfan, as well as the endosulfan sulfate transformation product, may reach water resources. Existing water monitoring data confirm the presence of endosulfan residues in surface and ground water on a qualitative basis (*EFED Risk Assessment for the Reregistration Eligibility Decision on Endosulfan, Nelson Thurman, et al., October 30, 2000*). Because endosulfan is persistent in neutral to acidic soils for months, the pesticide will be susceptible to transport via runoff for prolonged periods after initial application. With repeated applications, or even applications in consecutive years, endosulfan may accumulate in the soil, especially in acidic soils. Endosulfan is expected to be less persistent in alkaline soils due to its susceptibility to hydrolysis.

Its high affinity to sorb to soil indicates that endosulfan is likely to be associated predominantly with the sediment phase in runoff. Endosulfan reaching the water column, through spray drift or runoff, will have a propensity to sorb to benthic sediment, and this sediment may eventually become a source of endosulfan redistribution into the overlying waters. Published literature (details in *EFED Risk Assessment for the Reregistration Eligibility Decision on Endosulfan, Nelson Thurman, et al., October 30, 2000*) suggests that endosulfan may also be sorbed/taken up by macrophytes and algae, and released back into the water column when these plants die off. Because of its tendency to sorb onto soil, endosulfan should not be frequently detected in ground water; however, endosulfan is a persistent chemical, and available monitoring data have revealed endosulfan detections in wells. Aquifers below acidic soils are likely to be more vulnerable to endosulfan contamination than those below neutral or alkaline soils, due to the lack of hydrolysis under acidic conditions.

Endosulfan sulfate, the major transformation product identified in soil, is more persistent than the parent. Comparative studies indicate that endosulfan sulfate is similar in mobility to the parent endosulfan. The weight of evidence from available data suggests that endosulfan sulfate is a potential threat to the quality of both surface and ground waters.

Limited water monitoring data exist for endosulfan. Endosulfan was not included in the U.S. Geological Survey National Water Quality Assessment (NAWQA) program. The STORET database includes a variety of monitoring reports for the endosulfan isomers and for endosulfan sulfate. The results reported in the database vary in terms of data quality, sampling and analytical methods, detection limits, and level of quality assurance/quality control. Insufficient information exists with the reported studies to determine whether sampling occurred in actual endosulfan use areas or during times when endosulfan might potentially occur in water. Despite these limitations, the available studies have shown that endosulfan and its degradate, endosulfan sulfate, have contaminated numerous surface- and ground-water bodies throughout the United States. Both surface- and ground-water modeling simulations show that endosulfan and endosulfan sulfate may

reach ecologically significant water bodies as well as drinking water supplies.

4.3.1 Ground Water Resources

While both á- and â-endosulfan appear to be persistent in most laboratory studies, particularly in acidic to neutral soils, its high affinity to sorb onto soils suggests that it should not move extensively through the soil and vadose zone to ground water. The Agency believes that the potential for endosulfan to reach ground water is limited to acidic to neutral soils and aquifers where preferential flow may be a prevalent pathway to ground water or where the ground water is shallow and is overlain by highly permeable soils. Available evidence suggests that the transformation products – endosulfan sulfate and endosulfan diol – may be persistent. Endosulfan sulfate is similar in mobility to the parent endosulfan while endosulfan diol appears to be more mobile.

The Pesticides in Ground Water Database (USEPA OPP, 1992) reports detections of endosulfan, ranging from trace to ≤20 µg/L, in 1.3% of 2410 discrete samples (32 wells). Detections were reported in California, Maine, and Virginia. All sampling was conducted on or before the year 1989. The abbreviated nature of the PGWDB does not capture important factors such as depth of the water table, soil permeability, proximity of crops to wells, usage (application) of the chemical in the years prior to sampling, suitability of the analytical methodology used and/or limits of detection. Endosulfan sulfate was detected in 0.3% of the samples (6 out of 1969), with detections ranging from < 0.005 to 1.4 µg/L. The detections were reported in Indiana and New York. Sampling occurred at or prior to 1990. No data were available for endosulfan diol.

4.3.2 Surface Water Resources

Endosulfan can contaminate surface water through spray drift or runoff. The persistence of á- and â-endosulfan is sufficient to expect accumulation on soil after repeated applications and possible accumulation from year to year. Such persistence suggests that endosulfan will be available to move to surface waters via runoff for several months or longer after application. Its high affinity to sorb onto soil indicates that endosulfan may move primarily while adsorbed to eroding soil and will preferentially partition into the sediment fraction of the surface water system. Conditions which may favor runoff include poorly draining or wet soils with readily visible slopes toward adjacent surface waters, frequently flooded areas, areas overlaying shallow ground water, areas not separated from adjacent surface water with vegetated strips, and highly erodible soils cultivated using poor agricultural practices (such as conventional tillage).

The degradate endosulfan sulfate is probably formed in the soil and, due to its very high persistence, is likely to reach surface waters as well. Endosulfan diol may be formed in neutral to basic surface waters as a hydrolysis product. Comparative studies indicate that endosulfan sulfate will be similar in mobility to â-endosulfan, and thus have an affinity to bind to sediment, while endosulfan diol is likely to be more mobile than the parent.

A review of the STORET data for á- and â-endosulfan, unspecified endosulfan residues, and endosulfan sulfate showed numerous incidences of detections. The STORET data are not reliable enough to enable an accurate quantitative assessment of the endosulfan distribution throughout the U.S., but it does give some insight into where endosulfan is being found. Confirmed detections of one or more endosulfan residues were reported in 38 states. States that reported relatively high numbers of endosulfan detections (with respect to other reporting states) included California, Florida, Louisiana, Washington, Mississippi, and Ohio. An analysis of the monitoring data which reported detects for total endosulfan show a highly skewed distribution, as would be expected with monitoring data. The mean concentration is 0.17 µg/L, with a standard deviation of 0.98 µg/L. The 90^{th} percentile value was 0.31 µg/L and the median value was 0.03 µg/L. The mean STORET concentrations are not expected to exceed peak estimated environmental concentrations (EECs) predicted by the PRZM/EXAMS model because they do not necessarily represent the most vulnerable sites or sampled peak times. Little is known about actual sample conditions. In addition, the limits of detection vary widely depending on the purpose of the monitoring and the availability of analytical methods and equipment so that reported nondetections do not necessarily mean that endosulfan was not present where a non detect was reported.

The National Sediment Quality Survey (U.S. EPA, 1997) reported detections of endosulfan residues in stream sediments in 30 out of 76 watersheds in which endosulfan was analyzed. The watersheds occurred in 12 states, ranging from Rhode Island to California and from Mississippi to Michigan. As with the STORET data, one of the sources of data used in the survey, this summary provides more of a qualitative evaluation of the extent to which endosulfan may be found in the environment rather than a quantitative assessment of endosulfan occurrence.

4.3.3 Estimated Environmental Concentrations

Drinking water EECs for surface and ground water were determined from the PRZM/EXAMS and SCIGROW models, respectively. EFED based the á- and â-endosulfan drinking water EECs for surface-water sources on PRZM/EXAMS simulations with the maximum allowable application of endosulfan (1.0 lb a.i. / acre, 3 times per year) to a Mississippi cotton scenario with the standard index reservoir and percent crop area factor (PCA) included. Procedures for calculating the EECs followed the method described in the section on water assessment for ecological effects in *EFED Risk Assessment for the Reregistration Eligibility Decision on Endosulfan, Nelson Thurman, et al., October 30, 2000*: for the á- and â-endosulfan isomers, the output was adjusted by 70% for á-endosulfan and 30% for â-endosulfan; endosulfan sulfate concentrations were determined by multiplying the total endosulfan concentration by 0.55, the median ratio of endosulfan-sulfate to combined isomer concentrations found in the STORET database. Chemical-specific input parameters used for the PRZM/EXAMS simulations, as well as application-specific parameters for the cotton scenario used in the drinking water assessment are given in EFED's chapter. All other parameters were used according to standard EFED practice. Both the peak and chronic surface water EECs are well within the range of measured endosulfan concentrations in the EPA STORET database (where total endosulfan concentrations range from

less than the level of detection to a maximum peak of 180 µg/L). The groundwater EECs were generated with SCIGROW. For K_{oc} values greater than 10,000 ml/g, SCIGROW gives the default value of 0.006 ppb, regardless of other input parameters. The default SCIGROW value is within the range of reported groundwater detections of 0 to 20 ppb (USEPA OPP, 1992). Table 6 summarizes the estimated drinking water EECs for the á and â isomers of endosulfan and the degradate endosulfan sulfate.

Table 6. Tier 2 EECs for Endosulfan and Endosulfan Sulfate in Drinking Water

Isomer	Surface Water Acute[a] EEC	Surface Water Chronic[b] EEC	Ground Water EEC
á-endosulfan	3.5 µg/L	0.56 µg/L	--
â-endosulfan	1.7 µg/L	0.24 µg/L	--
total endosulfan (á+â)	5.2 µg/L	0.80 µg/L	0.006 µg/L
endosulfan sulfate	2.9 µg/L	0.45 µg/L	0.006 µg/L

[a] Acute EEC represents the upper 1-in-10 year peak concentration.
[b] Chronic EEC represents the upper 1-in-10 year mean annual concentration.

4.3.4 Drinking Water Levels of Comparison

Generally, the Agency calculates Drinking Water Levels of Comparison (DWLOC) for comparison to measured or modeled drinking water concentrations for the risk analysis. The DWLOC is the concentration in drinking water, as part of the aggregate exposure, that occupies no more than 100% of the PAD. The dietary exposure from food and the DWLOC together, cannot be greater than 100% of the PAD. Any measured or modeled drinking water estimates that are less than the DWLOC are not of concern.

The Agency has calculated DWLOCs for acute and chronic exposure to endosulfan in surface and ground water for the population subgroups; children 1-6 years (the most highly exposed subgroup), infants < 1 year, females 13-50 years, and the general U.S. population. To calculate the DWLOC for acute or chronic (non-cancer) exposure relative to an acute or chronic toxicity endpoint, the dietary food exposure (from DEEM™) was subtracted from the PAD to obtain the exposure to endosulfan in drinking water that would not be of concern.

An acute DWLOC ($DWLOC_{acute}$) was calculated using the following formulae:

$$DWLOC_{acute}\ (\mu g/L) = \frac{\text{acute water exposure (mg/kg/d) x body weight (kg)}}{\text{consumption (L/d) x } 10^{-3}\text{ mg/µg}}$$

acute water exposure (mg/kg/d) = [aPAD - acute food (mg/kg/d)]

The current Agency default body weight and consumption values are 10 kg and 1 liter/day, respectively, for all infants and children, 70 kg and 2 liters/day for adult males, and 60

kg and 2 liters/day for adult females. These default values and others are presently under review in the Agency (Office of Research and Development). If at a future time, the Agency decides to change the default assumptions used, the impact of the changes on the endosulfan risk assessment will be considered.

A chronic DWLOC ($DWLOC_{chronic}$) was calculated using the following formulae:

$$DWLOC_{chronic}\ (\mu g/L) = \frac{\text{chronic water exposure (mg/kg/d) x body weight (kg)}}{\text{consumption (L/d) x } 10^{-3}\ mg/\mu g}$$

chronic water exposure (mg/kg/d) = [cPAD - (chronic food + residential(ADD)(mg/kg/d))]

Where ADD = average daily dose

Residential exposures were not factored into the $DWLOC_{chronic}$ since no residential uses are being supported by the ETF, and are expected to be removed from all labels.

Table 7a. Endosulfan[a] Drinking Water Levels of Comparison (without Using Weighted FDA Data) for Acute Dietary Exposure

Population Subgroup	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/d) @ 99.9th percentile	Water Exposure (mg/kg/d)	$DWLOC_{acute}$ (μg/L)	Surface Water Peak EEC[b] (μg/L)	Ground Water EEC[b] (μg/L)
U.S. Population	0.015	0.0019	0.013	459	8.1	0.012
Females (13-50 yrs)	0.005	0.0016	0.0034	103	8.1	0.012
Infants <1 yr	0.005	0.0018	0.0032	32	8.1	0.012
Children 1-6 yrs	0.005	0.0035	0.0015	15	8.1	0.012

[a] Includes á-endosulfan, â-endosulfan, and endosulfan sulfate. [B] Estimated Environmental Concentrations.

Table 7b. Endosulfan[a] Drinking Water Levels of Comparison (Using Weighted FDA Data) for Acute Dietary Exposure

Population Subgroup	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/d) @ 99.9th percentile	Water Exposure (mg/kg/d)	$DWLOC_{acute}$ (μg/L)	Surface Water Peak EEC[b] (μg/L)	Ground Water EEC[b] (μg/L)

U.S. Population	0.015	0.0014	0.014	477	8.1	0.012
Females (13-50 yrs)	0.005	0.0012	0.0038	115	8.1	0.012
Infants <1 yr	0.005	0.0015	0.0035	35	8.1	0.012
Children 1-6 yrs	0.005	0.0026	0.0025	25	8.1	0.012

[a] Includes á-endosulfan, â-endosulfan, and endosulfan sulfate. [B] Estimated Environmental Concentrations.

Table 7c. Drinking Water Levels of Comparison (without Using Weighted FDA Data) for Chronic Dietary Exposure

Population Subgroup	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/d)	Max. Water Exposure (mg/kg/d)	$DWLOC_{chronic}$ (μg/L)	Surface Water Chronic EEC[b] (μg/L)	Ground Water EEC[b] (μg/L)
U.S. Population	0.006	0.000053	0.006	208	1.3	0.012
Females (13-50 yrs)	0.002	0.000039	0.002	59	1.3	0.012
Infants <1 yr	0.002	0.000061	0.0019	19	1.3	0.012
Children 1-6 yrs	0.002	0.00013	0.0019	19	1.3	0.012

[a] Includes á-endosulfan, â-endosulfan, and endosulfan sulfate. [B] Estimated Environmental Concentrations.

Table 7d. Drinking Water Levels of Comparison (Using Weighted FDA Data) for Chronic Dietary Exposure

Population Subgroup	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/d)	Max. Water Exposure (mg/kg/d)	$DWLOC_{chronic}$ (μg/L)	Surface Water Chronic EEC[b] (μg/L)	Ground Water EEC[b] (μg/L)
U.S. Population	0.006	0.000047	0.006	208	1.3	0.012
Females (13-50 yrs)	0.002	0.000034	0.002	59	1.3	0.012
Infants <1 yr	0.002	0.00006	0.0019	19	1.3	0.012
Children 1-6 yrs	0.002	0.00012	0.0019	19	1.3	0.012

[a] Includes á-endosulfan, â-endosulfan, and endosulfan sulfate. [B] Estimated Environmental Concentrations.

4.4 Residential Exposure/Risk Pathway

4.4.1 Home and Recreational Uses

As mentioned earlier, the ETF is not supporting any uses of endosulfan in or around the home, around public buildings or recreational areas, or on rights-of-way. Therefore, the Agency did not include the affected non-agricultural and residential uses in its revised risk assessment. However, labels exist that have not incorporated these changes and will need to be amended. Previous risk assessments showed unacceptable risks associated with home and recreational uses.

4.4.2 Other

The Agency's current approach for completing residential exposure assessments (when applicable) is based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed, such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

5.1 Overview

Risk is a function of exposure multiplied by hazard (Risk = Exposure x Hazard). Exposure may be measured or modeled, depending on the available data. Ideally the exposure data would be chemical-specific occupational or residential monitoring data, at-the-tap drinking water data, and close-to-the-plate food residue data on all crops. In the absence of an ideal data set, surrogate data, and other factors are incorporated into the exposure assessments (dietary and non-dietary) to present a reasonable exposure picture based on the best available data. The hazard portion of the risk equation has several layers of safety built into it to provide a cushion between exposure and the dose at which adverse effects were seen in an animal study. Generally, endpoints are based on the dose at which **no** observable adverse effect is seen in an animal study. This is the No Observable Adverse Effect Level (NOAEL). The Lowest Observable Adverse Effect Level (LOAEL) is the next highest dose in an animal study, up from the NOAEL, at which the adverse effect of concern is seen. Since the toxicity studies used for endpoint selection are conducted in animals, and there are differences between individual humans, additional uncertainty factors for inter- and intra-species variability are integrated into the hazard portion of the risk equation. Since the passage of the FQPA, an additional layer of protection is factored in (when appropriate) to provide an even greater safety cushion between exposure and toxic effects for particularly sensitive populations. It is in this light that expressions of risk (risk numbers) should be viewed with an understanding that they are not portrayals of imminent toxic effects to humans but as a measure of the distance between potential exposure and possible toxic effects.

In accordance with current HED policy (effective 03/11/99) the acute and chronic dietary endpoints are expressed as acute Population Adjusted Dose (aPAD) and chronic PAD (cPAD), and no longer as an adjusted Reference Dose (RfD).

$$\text{RfD} = \frac{\text{acute or chronic NOAEL}}{\text{Uncertainty Factor (UF)}}$$

Generally, an UF of 100 is applied for intra- and inter-species differences.

$$\text{PAD} = \frac{\text{acute or chronic RfD}}{\text{FQPA factor}}$$

The use of the PAD will apply whether the FQPA factor is retained (10x or 3x) or not (1x). When a PAD is used, such as in the dietary assessment, the risk is expressed as a percentage of the PAD which is equal to the measured exposure divided by the PAD and then multiplied by 100 or:

$$\text{Risk (\% PAD)} = \frac{\text{Exposure}}{\text{PAD}} \times 100$$

Occupational, residential (when applicable), and the aggregate risk (when appropriate) will still be expressed as the Margin of Exposure (MOE).

MOE = NOAEL (mg/kg/d
Exposure (mg/kg/d)

Current HED policy requires that FQPA safety factors be retained for dietary and non-occupational exposures, when appropriate, not occupational exposures (Memorandum, Special Report of the FQPA Safety Factor Committee, B. Tarplee and J. Rowland, April 15, 1998). Therefore, an MOE of $\geq$ 100 is needed in the occupational exposure risk assessment. In the case of endosulfan, an additional factor of 3x was applied for exposures exceeding 30 days and therefore, an MOE $\geq$ 300 is needed for exposures > 30 days.

Due to the availability of acceptable/guideline oral, dermal, and inhalation studies using endosulfan, the dietary and occupational risk assessments were conducted using route-specific endpoints. However, to fully characterize the hazard and potential risk from exposures to endosulfan, subchronic neurotoxicity and developmental neurotoxicity studies in rats, are requested by the HIARC. Protocols for these studies have been received but as of this writing, no data have been submitted. The acute dietary endpoint is based primarily on neurotoxicity. The neurotoxicity is believed to result from over-stimulation of the central nervous system. Characteristic clinical signs of endosulfan-induced neurotoxicity include, in part: hyperactivity, tonic contractions, involuntary muscle movements, pronounced sensitivity to noise and light, incoordination, seizures, and convulsions. These clinical signs are observed in humans accidentally exposed to endosulfan, and in animal studies of varying treatment durations following different routes of exposure and in different animal species. The chronic dietary, and short-, intermediate-, and long-term dermal and inhalation endpoints are based on the toxic effects observed in animals following subchronic or chronic exposure , and include: neurotoxicity, hematological effects, and nephrotoxicity. In some animal studies endosulfan inhibited plasma cholinesterase at the highest doses tested. Endosulfan is not a dermal sensitizer, nor is it mutagenic or carcinogenic ("Not Likely" a human carcinogen).

5.2 Acute Risk

5.2.1 Aggregate Acute Risk Assessment

The acute aggregate risk estimate includes the contribution of risk from dietary (food + drinking water) sources only. Acute risk estimates from exposures to food, associated with the use of endosulfan do not exceed the Agency's level of concern. The estimated acute dietary (food only) risk is 70% of the aPAD without using weighted FDA data, and 51% of the aPAD using weighted FDA data, at the 99.9th percentile for the most highly exposed population subgroup, children ages 1-6 years of age. The acute Tier 3 dietary risk analysis estimated the distribution of single day exposures for the overall U.S. population and certain population subgroups and evaluated exposure to endosulfan for each food commodity. The input values included the ARs, incorporating %CT and processing factors, for commodities on which endosulfan is used. Chemical-specific monitoring data on food were used for the majority of commodities. Where monitoring data were not available, translations from similar commodities or field trial data were used. No further refinements on exposures from food can be made at this time.

Though some chemical-specific water monitoring data are available, they are limited, and not at-the-tap data. Though they may be indicative of surface and ground water levels of endosulfan under limited conditions, the Agency believes that they are unsuitable to be quantitatively included in aggregate risk assessment. Therefore, estimated environmental concentrations (EECs) were calculated by EFED to estimate the potential contribution to the acute exposure from drinking water, and the EECs were compared to the acute DWLOCs.

5.2.2 Acute DWLOC Calculations

Taking into account the present uses and uses proposed in this action, the Agency can conclude with reasonable certainty that residues of endosulfan and endosulfan sulfate, combined, in drinking water would **not likely result in an acute dietary risk** to infants, children, and adults above the Agency's level of concern. The Agency based this determination on a comparison of estimated concentrations of endosulfan in surface waters to back-calculated "levels of comparison" for endosulfan in drinking water. The estimates of endosulfan in surface waters were derived from water quality models that used conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water, and were supplemented with limited monitoring data.

Modeled Tier 2 (PRZM/EXAMS) estimates of endosulfan and endosulfan sulfate concentrations in surface water, combined, were below the acute DWLOCs and are not of concern. The EECs calculated by EFED were based on the maximum allowable application of endosulfan (1 lb a.i/acre, 3 times/year) to a Mississippi cotton scenario with the standard index reservoir and percent crop area factor included. The available monitoring data indicate that 90th percentile values would not be expected to exceed peak EEC values. One should keep in mind that these estimates, as well as the available monitoring data, do not represent dilution from source to tap nor concentrations after drinking water treatment, and may actually be lower. Common drinking water treatment methods such as flocculation and sedimentation are known to remove some organochlorines but no endosulfan-specific treatment data are available.

The ground water EECs were generated using the SCIGROW (Tier 1) model applied to the Mississippi cotton scenario and appropriate fate and transport factors. The ground water estimates of endosulfan and endosulfan sulfate concentrations, combined, as well as available monitored concentrations, were below the acute DWLOCs and are not of concern.

5.3 Short- and Intermediate-term Aggregate Risk

Aggregate short- and intermediate-term risk includes the contribution of risk from dietary (food + water) and residential sources to the total risk. Since residential uses are not being supported by the ETF, exposures from these uses were not included in the risk assessment. Steps have already been taken to remove residential uses from endosulfan labels, but further steps are needed.

5.4 Chronic Risk

5.4.1 Aggregate Chronic Risk Assessment

Aggregate chronic (noncancer) risk estimates include the contribution of risk from dietary sources (food + water) and residential sources. However, as mentioned above, no residential uses are being supported. Chronic risk estimates from exposures to food, do not exceed the Agency's level of concern for the most highly exposed population subgroup, children ages 1-6 years of age. The chronic dietary (food only) risk estimate is 6% of the cPAD, with or without using weighted FDA data, for the most highly exposed population subgroup, children ages 1-6 years of age.

As in the acute aggregate assessment, EECs were calculated by EFED to estimate the potential contribution to the chronic exposure from drinking water, and the EECs were compared to the chronic DWLOCs.

5.4.2 Chronic DWLOC Calculations

Taking into account the present uses and uses proposed in this action, the Agency can conclude with reasonable certainty that residues of endosulfan and endosulfan sulfate, combined, in drinking water would **not likely result in a chronic dietary risk** to infants, children, and adults above the Agency's level of concern.

Modeled Tier 2 (PRZM/EXAMS) estimates of endosulfan and endosulfan sulfate concentrations in surface water, combined, were below the chronic DWLOCs and are not of concern. Again, the EECs calculated by EFED were based on the maximum allowable application of endosulfan to a Mississippi cotton scenario with the standard index reservoir and percent crop area factor included. Since the SCIGROW model does not allow for the generation of chronic ground water estimates, the acute values are used, resulting in a highly conservative estimate. Even these highly conservative ground water estimates of endosulfan and endosulfan sulfate concentrations, combined, were below the chronic DWLOCs and are not of concern.

6.0 CUMULATIVE RISK

Endosulfan, as well as its metabolite endosulfan sulfate, belong to the chlorinated cyclodiene (organochlorine) class of insecticide/acaricides. The Agency does not currently have data available to determine with certainty whether endosulfan or endosulfan sulfate have a common mechanism of toxicity with any other substances. For the purposes of this human health risk assessment, the Agency has not assumed that endosulfan or endosulfan sulfate have a common mechanism of toxicity with other pesticides. The Agency is in the process of formulating guidance for conducting cumulative risk assessment. When the guidance is completed, endosulfan and its metabolite(s) will be revisited to assess the cumulative effects of exposure to multiple organochlorines.

7.0 OCCUPATIONAL EXPOSURE

7.1 Handler

The Agency has determined that there are potential exposures to mixers, loaders, applicators, and other handlers during usual use-patterns associated with endosulfan. Based on the use patterns, 21 major occupational exposure scenarios were identified for endosulfan: (1a) mixing/loading liquid formulations for aerial application; (1b) mixing/loading liquid formulation for chemigation; (1c) mixing/loading liquid formulations for groundboom application; (1d) mixing/loading liquid formulations for airblast application; (1e) mixing/loading liquid formulations for rights-of-way sprays; (1f) mixing/loading liquid formulations for plant and root dip; (2a) mixing/loading wettable powders for aerial application; (2b) mixing/loading wettable powders for groundboom application; (2c) mixing/loading wettable powders for airblast application; (2d) mixing/loading wettable powder for rights of way spray application; (2e) mixing/loading wettable powders for plant and root dip; (3) applying sprays with aerial equipment; (4) applying sprays with a groundboom sprayer; (5) applying sprays with an airblast sprayer; (6) applying sprays with a rights-of-way sprayer; (7) applying dip treatment to roots, or whole plants; (8) mixing/loading/applying liquids with a low pressure hand wand; (9) mixing/loading/applying wettable powders with a low pressure handwand; (10) mixing/loading/applying liquids with a high pressure hand wand; (11) mixing/loading/applying liquids with backpack sprayer; and (12) flagging aerial spray applications.

On current endosulfan labels, personal protective equipment (PPE) requirements range from no PPE listed, to long sleeved shirt and long pants, waterproof gloves, shoes, socks, chemical resistant headgear, respirator with either an organic vapor removing cartridge with a prefilter or canister approved for pesticides. Mixers and loaders must also wear a chemical resistant apron.

In support of the reregistration process for endosulfan, AgrEvo USA submitted a worker exposure study for review by the Agency. The 1987 study, *Exposure of Mixer/Loader/ Applicators to Thiodan® 3EC Insecticide Applied to Fruit Trees by Airblast Equipment in*

California was originally submitted as MRID No. 410485-02. The registrant subsequently made revisions and resubmitted the study in 1990 as MRID No. 417152-01. The Agency determined that both the original and revised study do not meet Agency guidelines for acceptability under Subdivision U of the Pesticide Assessment Guidelines. Therefore, the data in MRIDs 410485-02 and 417152-01 were not used in the assessment. Instead, surrogate-based exposure assessments for each scenario, including airblast, were developed, where appropriate data were available, using the Pesticide Handlers Exposure Database (PHED) Version 1.1.

The registrant also submitted a risk assessment titled, *Evaluation of the Human Hazards and Risks Associated with the Application of Endosulfan*. dated March 1989 (MRID 410485-01). This submission was not used in this risk assessment for the following reasons: the exposure data used was from the above study (MRID 417152-01) which was found to be unacceptable, acres treated per day used were not justified and vary widely from the Agency standard values, and the monkey dermal penetration study which is critical in interpreting the biological monitoring data was not acceptable.

The Agency has reviewed Aventis' *Submission of an Application Exposure Assessment for Endosulfan and an Evaluation of Possible Endocrine Effects in Mammalian Species* dated August 4, 1999 (MRID 449391-01) and concludes that the submission does not follow standard Agency policies or use Agency standard default values. The Agency calculates high-end single-day exposures to occupational workers, based on maximum label application rates and standard values for the number of acres that can be treated in a single day by various types of agricultural equipment. These standard acres treated per day values are representative of most crops treated with endosulfan, including both low (strawberries) and high (potatoes) acreage crops, and are protective of commercial applicators who may treat multiple farms or fields in one day. Although the 1992 U.S. Census of Agriculture data used by Aventis does represent the national average crop acreage per farm, it is only representative of individual farmers and not of commercial applicators, who are likely to treat more acres in a day than individual growers.

The Agency notes that the revised dermal endpoints are based on the 21-dermal study in the rat for all exposure durations. For any duration longer than 30 days, an additional 3x safety factor was added to account for using a 21-day study for a duration of longer than 30 days. This study replaces the two-year chronic toxicity/carcinogenicity study in rats that was originally used to assess for intermediate-term dermal exposure. The Agency considered Aventis' submission for inclusion in the endosulfan assessment, but because of the aforementioned discrepancies, it was not included in this assessment.

Handler exposure assessments were completed using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) in an attempt to achieve an appropriate margin of exposure. The baseline scenario generally represents a handler wearing long pants, a long-sleeved shirt, no respirator, and no chemical-resistant gloves (there are exceptions pertaining to the use of gloves, and these are noted).

It is desirable that short-term occupational risks, expressed as margins of exposure

(MOEs), be $\geq$ 100. MOEs below 100 are of concern. In accordance with current Agency guidance, the FQPA factor is not retained for the occupational risk assessment (Memorandum, Special Report of the FQPA Safety Factor Committee, B. Tarplee and J. Rowland, April 15, 1998). Dermal and inhalation risks for handlers were assessed separately since the end effects for the toxicological endpoints chosen for these exposures are dissimilar and Agency policy prevents aggregation of the risks (inhalation plus dermal) if the toxicological effects are not the same. Handler exposures to endosulfan are expected to be short-term only (1 day to one month).

Of the 21 identified occupational handler exposure scenarios, 13 of them are a risk of concern, having calculated MOEs less than the target MOE of 100, at the highest level of mitigation for **short-term dermal** exposure. For **short-term inhalation** exposure, 4 of the 21 identified occupational handler exposure scenarios are a risk of concern, having calculated MOEs less than the target MOE of 100, at the highest level of mitigation. See Table 9a, *Summary of Occupational Handler Risks to Endosulfan*. Three scenarios lack data to assess their risk. Data are needed to assess the following occupational handler scenarios: applying dip treatments to trees and roots or whole plants and mixing/loading/applying wettable powders with a backpack sprayer and a high pressure handwand.

Several issues must be considered when interpreting the occupational exposure risk assessment. These include:

- Several generic protection factors (PF) were used to calculate handler exposures (e.g., 90% PF over baseline for inhalation unit exposure to account for use of an organic vapor removing respirator).

- Low confidence data, based on PHED grading criteria, were used to calculate the risks to handlers from the following scenarios for any body part and/or level of mitigation: Mixing/loading wettable powders, applying sprays with an airblast sprayer (enclosed cabs), applying sprays with a rights of way sprayer, mixing/loading/applying liquids and wettable powders with a low pressure handwand, mixing/loading/applying liquids with a high pressure handwand and backpack sprayer, and flagging aerial applications.

7.2 Postapplication

The Agency has determined that there are potential short- and intermediate-term postapplication exposures to individuals entering treated fields. Current endosulfan labels show a restricted entry interval (REI) requirement of 24 hours with the following early entry PPE required: coveralls, waterproof gloves, shoes, socks and chemical resistant headgear for overhead exposures.

For the purpose of conducting this assessment, crops were grouped in order to assign the most representative dislodgeable foliar residue (DFR) data to the crops. The crop groups listed below were chosen because appropriate residue data were available (MRID 444031-02). The crop groups and corresponding surrogate residue data sources are as follows:

- *Tree Crops*: DFR data for peaches were used, based on a study using an application rate of 3 lb ai/acre. This application rate is consistent with the application rates for most fruit and nut trees. For the crops where the application rates were not 3 lbs ai/acre, the DFR data were adjusted (linear) to the appropriate application rate for the individual crops.

- *Grape Harvesting, Girdling and Irrigating*: This scenario was based on DFR data for grapes using an application rate of 1.5 lbs ai/acre. This is the labeled application rate for grapes.

- *Field Crops*: DFR data for melons were used and were assumed to be representative of exposure from postapplication activities associated with all the remaining crops registered for endosulfan except for grapes and tree crops. The DFR data were based on an application rate of 1 lb ai/acre. However, most of the labeled application rates for these crops range from 0.25 to 3 lb ai/acre. Thus, the DFR data were adjusted (linear) to the appropriate application rate for the individual crops.

A DFR study was conducted for endosulfan and its metabolites, â-endosulfan and endosulfan sulfate. The study evaluated dislodgeable residue dissipation for endosulfan applied to peaches, grapes, and melons (MRID No. 444031-02). In summary, the DFR study completed in support of the regulatory requirements for endosulfan did not completely meet the criteria contained in Subdivision K of the Pesticide Assessment Guidelines. Despite the uncertainties associated with the study (see *Second Revision of "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Endosulfan, Renee Sandvig, January 2, 2001*), the Agency used the data from the DFR study in assessing the appropriate postapplication exposure from agricultural activities using endosulfan.

A second DFR study (MRID 403039-01) was conducted for endosulfan. This study examined DFR residues on apples, apricots, processing tomatoes, and cherry tomatoes. However, this study was unacceptable and was not used in estimating the postapplication exposures. All postapplication exposure estimates were based on MRID No. 444031-02. It should be noted that the half lives from the unacceptable study were similar to or higher than the half lives from the study used to determine postapplication exposure in this assessment. This indicates that the DFR data from the unacceptable study would result in restricted entry interval calculations similar to or even longer than the ones calculated in this assessment.

Short-term Postapplication Exposures and Risks

A dose and a MOE are determined from the declining predicted DFR values until the target MOE of 100 is reached for every crop for both the emulsifiable concentration and wettable powder formulations. The NOAEL used in the short-term dermal assessment is 3.0 mg/kg/day and the target MOE is 100 for the short-term exposure duration. For the emulsifiable concentrate formulation, the day after treatment when the calculated MOE equals or exceeds the target MOE of 100 ranges from 2 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting to 28 days for detasseling corn at an application rate of 1.5 lbs ai/acre. For the wettable powder formulation, the day after treatment when the calculated

MOE equals or exceeds the target MOE of 100 ranges from 8 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting to 49 days for girdling grapes at an application rate of 1.5 lbs ai/acre. Occupational postapplication risks from short-term dermal exposure are of concern.

Intermediate-term Postapplication Exposures and Risks

Intermediate-term postapplication exposure is expected because endosulfan is registered for a large number of crops and postapplication workers maybe exposed continuously to endosulfan, particularly when application is repeated every seven days for two to three applications. The NOAEL used in the intermediate-term dermal assessment is 3.0 mg/kg/day and the target MOE is 300. For short-term postapplication exposure, the worker is assumed to be exposed to the residue level that occurs on the day the calculated MOE reaches the target MOE from that day on to possibly the entire exposure duration, without factoring declining residues. It is possible for a worker to re-enter multiple fields, encountering a high residue level in each field. For example, the target MOE was reached on day 8 for the wettable powder formulation on peppers. Therefore, a worker could enter the field on day 8 and the worst case exposure would be that the worker is exposed to day 8 residues for up to 30 days. This exposure would be not be considered to have a risk of concern, since the target MOE was reached on day 8.

Since the intermediate-term exposure duration is 30 days to several months, it would be improbable that a worker would contact the same residue level for the entire exposure duration. Instead, an average of 30 days of predicted residues is determined from the day the short-term duration does not have a risk of concern. The probable worst case scenario for intermediate-term exposure would be that a worker would be exposed to an average of the residues that are possible during the 30 day decline in the short-term exposure duration. If this residue value does not yield a target MOE of 300 for intermediate-term, then the average residue value is shifted one day, until the target MOE is reached. Then the day when there is not risk of concern for intermediate-term exposure would be the first day of the average residue period. For example, since the worker in the previous example could re-enter the field on day 8 for the short-term duration, then the residues from day 8 to day 38 would be averaged. This value must result in a target MOE of $\geq$ 300, for the intermediate-term duration to not be of concern on the same day as the short-term duration (day 8). If this average residue value results in an MOE of less than the target MOE, then the decline period is shifted to 9 to 39 days. This is done until the target MOE is reached for the average residue value. If it was reached for the 9 to 39 day period, then 9 days would be the day that the intermediate-term duration would not have a risk of concern.

For the emulsifiable concentrate formulation, the day after treatment when the calculated MOE equals or exceeds the target MOE of 100 ranges from 2 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting, to 28 days for detasseling corn at an application rate of 1.5 lbs ai/acre. For the wettable powder formulation, the day after treatment when the calculated MOE equals or exceeds the target MOE of 100 ranges from 8 days for peppers, eggplant and tomatoes at an application rate of 1 lb ai/acre for activities such as hand harvesting, to 52 days for girdling grapes at an application rate of 1.5 lbs ai/acre. Occupational intermediate-term postapplication risks from dermal exposure are of concern. See

Table 9b, *Summary of Postapplication Exposure*.

7.3 Non-occupational Exposures

Non-occupational exposures to endosulfan, such as from spray drift, were not included in this assessment. The Agency is developing policy on how to appropriately assess potential risks from spray drift, and after the policy is in place, the Agency will reevaluate the potential non-occupational risks from exposure to endosulfan.

7.4 Incident Data

The Agency has reviewed the Incident Data System (IDS), the Poison Control Center, the California Department of Food and Agriculture (Department of Pesticide Regulation), and the National Pesticide Telecommunications Network (NPTN) databases for reported incident information for endosulfan (Blondell, J., 2000). A number of accidental human poisonings from exposure to endosulfan in both occupational and residential settings have been reported. The data from these sources often lacked specific information on the extent of exposure and the circumstances of exposure. Collectively, however, the incidence information indicate definite poisoning risks from misuse of products that contain endosulfan, or from not wearing personal protective equipment. Available incidence data clearly show that flagrant misuse of concentrated formulations of endosulfan could result in exposures that cause serious, life-threatening poisoning, or permanent neurological toxicity. Both handler and postapplication workers have experienced moderate systemic poisoning as a result of exposure to endosulfan. In addition, there appears to be a consistent risk of skin rash or irritation among field workers who have substantial contact with treated foliage. Endosulfan does not appear to pose risks of concern from spray drift exposure. Results from the incidence data indicate that all skin surfaces should be protected when workers are handling endosulfan formulations, particularly concentrated formulations. Restricted entry intervals sufficient to minimize substantial contact with treated foliage are warranted.

8.0 DATA NEEDS/LABEL REQUIREMENTS

Additional data needs/requirements have been identified in the referenced discipline chapters and are summarized here.

8.1 Toxicology

Two additional toxicity studies are warranted as a result of the uncertainties regarding increased sensitivity of infants and children to endosulfan following prenatal or postnatal exposure. These toxicity studies are 1) a subchronic neurotoxicity study (870.6200) and 2) a developmental neurotoxicity (870.6300) assay. Note: Protocols for these studies have been received and reviewed. The data have not been submitted.

8.2 Product Chemistry

Product chemistry data requirements that remain outstanding for the 7 registered technicals include specific details pertaining to the process used to manufacture endosulfan: a statement as to whether the process is batch or continuous; the duration of each step of the process; the relative amounts of the materials used; a description of the manufacturing equipment; a more complete description of the reaction conditions controlled during each step of the process; a description of the sampling regimen and quality control procedures necessary to assure product consistency; an updated confidential statement of formula (CSF) including nominal concentrations for the active ingredient and impurities present in concentrations greater than 0.1%.

8.3 Residue Chemistry

The existing residue chemistry database is incomplete. Label revisions are required for many crops in order to reflect the parameters of use patterns for which residue data are available. Most of the required label revisions pertain to the establishment of preharvest intervals.

The reregistration requirements for magnitude of the residue in/on the following RACs have not been fulfilled, and field trial data are required: barley flour, hay, bran and pearled barley; oat forage, hay, flour, and rolled oats; rye forage, flour, and bran; sugar cane; wheat forage, hay, aspirated grain fractions.

8.4 Occupational Exposure

Data gaps exist for the following scenarios:

- Applying dip treatments to trees and roots or whole plants.
- No exposure data exist for mixing/loading/applying wettable powders with a high pressure handwand and a backpack sprayer. These two scenarios are expected to have risks of concern since similar scenarios assessed in this document, mixing/loading wettable powders and mixing/loading/applying liquids with a high pressure handwand, have risks of concern.

If the registrant is interested in refining the Agency's calculated REIs, additional DFR data and/or worker exposure monitoring data may be submitted.

Table 8. Use Pattern Summary for Endosulfan.

Formulation types (% ai)	Equipment used	Use sites	Application Rates Range	Timing and Frequency of Application
Technical grade manufacturing product (95 percent active ingredient [ai]), emulsifiable concentrate (9 percent to 34 percent active ingredient), and a wettable powder (1 percent to 50 percent active ingredient).	Commercial use: groundboom sprayer, fixed-wing aircraft, chemigation (potatoes only), airblast sprayer, rights of way sprayer, low pressure handwand, high pressure handwand, backpack sprayer, and dip treatment.	Alfalfa (seed only), barley, beans (dry and succulent), blueberries, broccoli, brussel sprouts, cabbage, carrots, cauliflower, celery, clover (seed only), collards, cotton, corn (fresh only), cucumbers, eggplants, grapes, kale, kohlrabi (seed only), lettuce, melons, mustard greens, oats, peas, peppers, pineapples, potatoes, pumpkins, radish (seed only), rutabaga (seed only), rye, spinach, squash, sweet potatoes, strawberries, tobacco, tomato, turnip, wheat, apples, apricots, almonds, cherries, filberts, macadamia nuts, nectarines, pecans, peach, pear, plums, prunes, walnuts, shade trees, citrus (non-bearing and nursery stock), shrubs, nursery stock, Christmas tree plantations, and Root dip (cherry, peaches, and plum roots and crowns, whole strawberry plants).	Application rates range from 0.5 lbs ai/acre for clover to 3 lbs ai/acre for apricots.	Endosulfan can be applied at any time of the growing season. It may be applied from 1 to 6 times a year, with an average of 2 times per year.

Table 9a. Summary of Occupational Handler Risks to Endosulfan

Exposure Scenario (Scenario #)	Crop Type/Use[a]	Range of Application Rates (lb ai/A)[b]	Amount Handled per Day[c]	Baseline[f]		Additional PPE[g]		Engineering Controls[h]	
				Dermal MOE[d]	Inhalation MOE[e]	Dermal MOE[d]	Inhalation MOE[e]	Dermal MOE[d]	Inhalation MOE[e]
Mixer/Loader Exposures									
Mixing/Loading Liquid Formulations for Aerial Application (1a)	clover	0.5 lb ai/A	350 Acres	0.41	67	71	670	140	-
	tobacco	2.5 lb ai/A		0.083	13	14	130	**28**	-
	pecans	7.5 lb ai/A		0.028	4	5	44	**10**	**64**
	small grains	0.75 lb ai/A	1200 Acres	0.08	13	14	130	**27**	-
	cotton	1.5 lb ai/A		0.04	7	7	65	**14**	**94**
Mixing/Loading Liquid Formulation for Chemigation (1b)	potatoes (Idaho)	1.0 lb ai/A	350 Acres	0.21	33	35	330	**70**	-
Mixing/Loading Liquid Formulations for Groundboom Application (1c)	clover	0.5 lb ai/A	80 Acres	2	290	310	-	-	-
	tobacco	2.5 lb ai/A		0.36	58	62	580	120	-
	small grains	0.75 lb ai/A	200 Acres	0.48	78	82	780	160	-
	cotton	1.5 lb ai/A		0.24	39	41	390	**81**	-
Mixing/Loading Liquid Formulations for Airblast Application (1d)	Ornamental Trees/Shrubs	1.0 lb ai/A	40 Acres	2	290	310	-	-	-
	hazelnuts	2.0 lb ai/A		0.91	150	150	-	-	-
	pecans	7.5 lb ai/A		0.24	39	41	390	**81**	-
Mixing/Loading Liquids for Rights of Way Spray Application (1e)	grapes	0.005 lb ai/gal	1000 Gallons	14	2300	2500	-	-	-
	cherry	0.04 lb ai/gal		1.8	290	310	-	-	-
Mixing/Loading Liquids for Plant and Root Dip (1f)	cherry, peach and plums	0.05 lbs ai/gal	100 Gallons	14	2300	2500	-	-	-
Mixing/Loading Wettable Powders for Aerial Application (2a)	beans	1.0 lb ai/A	350 Acres	0.16	0.93	5	10	**61**	170
	sweet potato	2.0 lb ai/A		0.081	0.47	2	5	**31**	**83**

Table 9a. Summary of Occupational Handler Risks to Endosulfan

Exposure Scenario (Scenario #)	Crop Type/Use[a]	Range of Application Rates (lb ai/A)[b]	Amount Handled per Day[c]	Baseline[f]		Additional PPE[g]		Engineering Controls[h]	
				Dermal MOE[d]	Inhalation MOE[e]	Dermal MOE[d]	Inhalation MOE[e]	Dermal MOE[d]	Inhalation MOE[e]
	peach	3.0 lb ai/A		0.054	0.31	1.5	3	**20**	**56**
	small grains	0.75 lb ai/A	1200 Acres	0.063	0.36	2	4	**24**	**65**
	cotton	1.5 lb ai/A		0.032	0.18	1	2	**12**	**32**
Mixing/Loading Wettable Powders for Groundboom Application (2b)	beans	1.0 lb ai/A	80 Acres	0.71	4	20	41	270	730
	sweet potato	2.0 lb ai/A		0.35	2	10	20	130	360
	small grains	0.75 lb ai/A	200 Acres	0.38	2	11	22	140	390
	cotton	1.5 lb ai/A		0.19	1	5	11	**71**	190
Mixing/Loading Wettable Powders for Airblast Application (2c)	Ornamental Trees/Shrubs	1.0 lb ai/A	40 Acres	1.4	8	40	81	540	1500
	hazelnuts	2.0 lb ai/A		0.71	4	20	41	270	730
	peaches	3.0 lb ai/A		0.47	3	13	27	270	490
Mixing/Loading Wettable Powders for Rights of Way Spray Treatment (2d)	grapes	0.005 lb ai/gal	1000 Gallons	11	65	320	650	-	-
	walnut	0.02 lb ai/gal		3	16	81	160	1100	-
Mixing/Loading Wettable Powders for Plants and Root Dip (2e)	cherry, peach, and plum	0.05 lb ai/gal	100 Gallons	11	65	320	650	-	-
Applicator Exposures									
Applying Spray with Aerial Equipment (3)	clover	0.5 lb ai/A	350 Acres	See Eng. Controls	See Eng. Controls	See Eng. Controls	See Eng. Controls	240	1200
	tobacco	2.5 lb ai/A						**48**	240
	pecans	7.5 lb ai/A						**16**	**78**
	small grains	0.75 lb ai/A	1200 Acres					**47**	230
	cotton	1.5 lb ai/A						**23**	110
Applying Sprays with a Groundboom Sprayer (4)	clover	0.5 lb ai/A	80 Acres	380	470	-	-	-	-
	tobacco	2.5 lb ai/A		75	95	95	950	210	-
	small grains	0.75 lb ai/A	200 Acres	100	130	-	-	-	-
	cotton	1.5 lb ai/A		50	63	64	630	140	-
Applying Sprays with an Airblast Sprayer (5)	ornamental trees	1.0 lb ai/A	40 Acres	15	78	24	780	280	-
	hazelnuts	2.0 lb ai/A		7.3	39	12	390	140	-
	pecans	7.5 lb ai/A		2	10	3	100	**37**	-

Table 9a. Summary of Occupational Handler Risks to Endosulfan

Exposure Scenario (Scenario #)	Crop Type/Use[a]	Range of Application Rates (lb ai/A)[b]	Amount Handled per Day[c]	Baseline[f]		Additional PPE[g]		Engineering Controls[h]	
				Dermal MOE[d]	Inhalation MOE[e]	Dermal MOE[d]	Inhalation MOE[e]	Dermal MOE[d]	Inhalation MOE[e]
Applying Sprays with a Rights of Way Sprayer (6)	grapes	0.005 lb ai/gal	1000 Gallons	32	720	140	-	NA	NA
	cherries	0.04 lb ai/gal		4	90	18	900	NA	NA
Applying Dip Treatment to Roots, or Whole Plants (7)	cherry, peach, plum roots	0.05 lb ai/gal	100 gallons	No Data	No Data	ND	ND	ND	ND
Mixer/Loader/Applicator Exposure									
Mixing/Loading/Applying Liquid Formulations with a Low Pressure Handwand (8)	tobacco (drench)	0.005 lb ai/gal	40 Gallons	11	2300	2800	-	NA	NA
	tomato (greenhouse)	0.01 lb ai/gal		5	1200	1400	-	NA	NA
	cherries	0.04 lb ai/A		1.3	290	350	-	NA	NA
Mixing/Loading/Applying Wettable Powders with a Low Pressure Handwand (9)	tomato/ tobacco	0.005 lb ai/gal	40 Gallons	36	64	170	640	NA	NA
	walnut	0.02 lb ai/gal		9	16	**42**	160	NA	NA
Mixing/Loading/Applying Liquid with a High Pressure Handwand (10)	tobacco (drench)	0.005 lb ai/gal	40 Gallons	12	23	**26**	230	NA	NA
	tomato (greenhouse)	0.01 lb ai/gal		6	12	**13**	120	NA	NA
	cherries	0.04 lb ai/A		1.5	3	**3**	**29**	NA	NA
Mixing/Loading/Applying Liquid with Backpack Sprayer (11)	tobacco (drench)	0.025 lb ai/gal	40 Gallons	420	2300	-	-	NA	NA
	tomato (greenhouse)	0.01 lb ai/gal		210	1200	-	-	NA	NA
	cherries	0.04 lb ai/A		53	290	**82**	-	NA	NA
Flagger Exposures									
Flagging Aerial Spray Applications (12)	clover	0.5 lb ai/A	350 Acres	110	230	-	-	-	-
	tobacco	2.5 lb ai/A		22	46	24	460	1100	-
	pecans	7.5 lb ai/A		7	15	8	150	360	-

Footnote:

a Crops named are index crops which are chosen to represent all other crops at or near that application rate for that use. See the application rates listing in the use summary section of this document for further information on application rates used in this assessment.

b Application Rates are based on the maximum application rates listed on the endosulfan labels.

c Amount handled per day are from Science Advisory Council on Exposure's Policy # 9.

d Short- term Dermal MOE = Short- term NOAEL (mg/kg/day)/ Daily Dermal Dose (mg/kg/day).

e Short-term MOE = Short- term NOAEL (mg/kg/day)/ Daily Inhalation Dose (mg/kg/day).

f Baseline clothing: long pants, long sleeved shirt, shoes, socks.

g Additional PPE clothing: Baseline clothing plus organic vapor respirator, plus coveralls, and chemical resistant gloves.

h Engineering controls: Enclosed mixing/loading, closed cab, truck or cockpit. Baseline level clothing. Chemical resistant gloves for airblast sprayer.

- Scenario's calculated MOE exceeds the target MOE at the previous level of mitigation. (MOE > 100)

NF = Not feasible for this scenario (no available engineering controls).ND = No data.

Bolded MOE values show a risk of concern at the highest possible level of mitigation for the corresponding scenario.

Table 9b. Summary of Postapplication Exposure.

Crop[a]	Maximum Label Application Rate (lbs ai/acre)[d]		Transfer Coefficient[e] (cm^2/hr)	Activity[f]	Short-term Exposure		Intermediate-term Exposure	
					Day after Application When MOE 100[g]		First day of Decline Period When MOE 300[h]	
	WP[b]	EC[c]			WP[b]	EC[c]	WP[b]	EC[c]
Table Grapes / Raisins	1.5	1.5	10,000	Cane turning and tying, and girdling	49	17	**52**	17
Juice Grapes	1.5	1.5	5,000	Tying, training, hand harvesting, hand pruning, and thinning.	39	11	**42**	11
Grapes, Table and Juice	1.5	1.5	1,000	Scouting and irrigating	17	0	**20**	0
Apple, Apricot, Cherry, Nectarines, Peach, Pear, Plum, Prune, and Christmas Trees.	3	3	8,000	Thinning, staking, topping, training, and hand harvest	30	17	30	17
Ornamental Trees / Shrubs including Evergreen Trees and Non-bearing Citrus Trees.	3	3	3,000	Hand pruning and seed cone harvesting	20	6	20	6
Apple, Apricot, Cherry, Nectarines, Peach, Pear, Plum, Prune, Ornamental Trees / Shrubs including Evergreen Trees, Non-bearing Citrus Trees. and Christmas Trees.	3	3	1,000	Scouting and irrigating	8	0	8	0
Macadamia nuts and Pecans	NA	7.5	2,500	Hand harvesting, pruning, and thinning	NA	14	NA	**18**
			500	Scouting and irrigating	NA	0	NA	0
Hazelnut, Almonds and Walnut	2	2.5	2,500	Hand harvesting and pruning	14	2	14	**7**
			500	Scouting and irrigating	0	0	0	0
Blueberries, Kohlrabi, Broccoli, and Cabbage.	2	2	5,000	Hand harvesting, pruning, thinning, and irrigating.	24	20	24	20
Kohlrabi, Broccoli, and Cabbage.	2	2	4,000	Scouting and irrigating	22	19	22	19
Blueberries	2	2	1,000	Scouting and irrigating	12	8	12	8
Brussel Sprouts and Cauliflower	1	1	5,000	Topping, irrigating, hand harvesting, and tying.	19	15	19	15
			4,000	Scouting and irrigating	17	13	17	13
Corn	1.5	1.5	17,000	detasseling	31	28	31	28
			1,000	Scouting and irrigating	10	5	10	5
Cucumber, Melons, Pumpkin, Squash, Beans, Peas, Celery, Lettuce, Spinach, and Carrots.	1	1	2,500	Hand harvesting, pruning, thinning, turning, and leaf pulling	14	9	14	9

Crop[a]	Maximum Label Application Rate (lbs ai/acre)[d]		Transfer Coefficient[e] (cm^2/hr)	Activity[f]	Short-term Exposure		Intermediate-term Exposure	
					Day after Application When MOE 100[g]		First day of Decline Period When MOE 300[h]	
	WP[b]	EC[c]			WP[b]	EC[c]	WP[b]	EC[c]
Alfalfa, Barley , Clover, Oats, Rye, Wheat, White Potatoes, Cucumber, Melon, Pumpkin, Squash, Bean, Peas, Celery, Lettuce, and Spinach.	1	1	1,500	Scouting and irrigating	10	5	10	5
Carrots	1	1	300	Scouting and irrigating	0	0	0	0
Pepper, Eggplant, and Tomato	1	1	1,000	Hand harvesting, staking, tying, pruning, thinning, and training.	8	2	8	2
			700	Scouting and irrigating	5	0	5	0
Pineapple	2	2	1000	Hand harvesting	12	8	12	8
			500	Scouting and irrigating	7	2	7	2
Strawberry	2	2.5	1,500	Hand harvesting, pinching, pruning, and training.	15	13	15	13
			400	Scouting and irrigating	6	2	6	2
Cotton, Collard Greens, Kale, Mustard Greens, Sweet Potato, Radish, Rutabaga, and Turnip.	2	2	2500	Hand harvesting, pruning, and thinning.	18	15	18	15
Cotton, Collard Greens, Kale, Mustard Greens and Sweet Potato.	2	2	1,500	Scouting and irrigating	15	11	15	11
Radish, Rutabaga, and Turnip.	2	2	300	Scouting and irrigating	4	0	4	0
Tobacco	1.5	3	2,000	Hand harvesting, pruning, striping, thinning, topping, and hand weeding	15	16	15	16
			1,300	Scouting and irrigating	12	13	12	13

Footnotes:

NA = Not applicable (formulation use does not exist for the crop)

a Crops were grouped according to similar application rates, transfer coefficients, and surrogate DFR data sources.

b WP = wettable powder formulation

c EC = emulsifiable concentrate formulation

d maximum application rates as stated on current endosulfan labels.

e Transfer Coefficients from Science Advisory Council on Exposure Policy 3.1[17]

f Activities are from Science Advisory Council on Exposure Policy 3.1.[17] Each activity many not occur for every crop listed in group.

g Day after application when the calculated MOE is greater than the target MOE of 100. The short-term target MOE of 100.

h First day of decline period (30 days) when average residues result in an MOE > 300, which would be the first day that would not have a risk of concern. Bolded values denote when intermediate-term DAT not resulting in a risk of concern is different than short term DAT not resulting in a risk of concern..

9.0 REFERENCES AND ATTACHMENTS

9.1 Attachments

Assessment of the Dietary Cancer Risk of Hexachlorobenzene and Pentachlorobenzene as impurities in Chlorothalonil, PCNB, Picloram, and several other pesticides. William Smith, February 26, 1998.

Endosulfan: Evaluation of Registrant Submission, *Endosulfan: Evaluation of Possible Endocrine Effects in Mammalian Species*. Elizabeth Mendez, December 11, 2000.

Endosulfan, Product Chemistry Chapter for Reregistration Eligibility Decision. Ken Dockter, December 18, 1998.

Endosulfan: Re-Evaluation of Toxicology Endpoint Selection for Dermal and Inhalation Risk Assessments; Report of the Hazard Identification Assessment Review Committee. Nicole Paquette, January 31, 2000.

Endosulfan-Report of the FQPA Safety Factor Committee. Brenda Tarplee, November 20, 1998.

Quantitative Usage Analysis for Endosulfan. Steven Nako, October 13, 1999.

Quantitative Usage Analysis for Endosulfan, Updated. David Donaldson, September 10, 2000.

Review of Endosulfan Incident Reports. Jerome Blondell and Monica Spann, January 18, 2000.

Revised Anticipated Residues, Acute and Chronic Dietary Exposure Analyses for Endosulfan. Sherrie Kinard, December 15, 2000.

Revised Residue Chemistry Chapter for the Endosulfan Reregistration Eligibility Decision (RED) Document. John Punzi, January 3, 2001.

Second Revision of *Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Endosulfan*. Renee Sandvig, January 2, 2001.

Toxicology Chapter for Endosulfan RED. Nicole Paquette and David Liem, November 22, 1999.

9.2 References

CDFA. 1987. California Department of Food and Agriculture; A Study to Establish Degradation Profiles for Six Pesticides (triforine, endosulfan, chlorothalonil, sulfotepp, dodemorph acetate, and daminozide) Used on Ornamental Foliage in San Diego County, California During Fall 1986.

Cooper, R.L.; and Kavlock, R.J. 1997. Endocrine Disruptors and Reproductive Development: a Weight-of Evidence Overview. Journal of Endocrinology 152: 159-166.

Crisp, T.M. et al. 1998. Environmental Endocrine Disruption: An Effects Assessment and Analysis. Environmental Health Perspectives 106: 11-56.

EFED Risk Assessment for the Reregistration Eligibility Decision on Endosulfan (Thiodan®). Nelson Thurman, et al., October 30, 2000.

Lakshmana, M.K.; and Raju, T.R. 1994. Endosulfan induces small but significant changes in the levels of noradrenalin, dopamine and serotonin in the developing rat brain and deficits in the operant learning performance. Toxicology 91(2): 139-150.

USEPA 1985. Health Assessment Document for Chlorinated Benzenes: Final Report. United States Environmental Protection Agency, Washington, D.C. EPA 600/8-84/016F (January, 1985). See also Federal Register: vol 49, pages 23440-23441 (June 6, 1984).

Williams, D.T.; Denley, H.V.; and Lane, D.A. 1980. On Site Determination of Sulfotepp Air Levels in a Fumigating Greenhouse. American Industrial Hygiene Association Journal 4: 647-651.

Williams, L.H. 1978. Dissipation of Sulfotepp and Nicotine in a Greenhouse Atmosphere Following Their Use as Fumigants. Journal of Environmental Science and Health B13(3): 235-241.